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BULLETIN OF
THE NEW YORK ACADEMY
OF MEDICINE

OCTOBER 1941

NEWER SURGERY OF THE HEART AND LARGE VESSELS: MEDICAL ASPECTS*

H. M. MARVIN

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IT was with deep gratification that I received and accepted the invitation to participate in the exercises of this evening, and I wish first of all to express my lively appreciation of the honor and the privilege of appearing once more in this hall as one of your speakers. It is surely unnecessary to tell a New York audience that my pleasure is all the greater because of the distinguished company in which I appear. I strongly suspect that my presence this evening is due to the fear, in the minds of your Committee, that if Dr. Andrus† were allowed to speak without opposition, as it were, his eloquence and enthusiasm might unintentionally lead many of you to magnify the advantages and minimize the disadvantages of surgery. I assume that mine was to be the voice of conservatism, and my function was to warn you urgently against the wiles and blandishments of our surgical brethren!

But if there was some such thought as this in the minds of those who arranged the program, circumstances have conspired to prevent its fulfillment. Through a series of misfortunes, of which illness was

* Presented at the Stated Meeting of The New York Academy of Medicine, February 6, 1941.
† William De Witt Andrus, Associate Professor of Surgery, Cornell University Medical College.

the chief one, Andrus and I were prevented from meeting, or even writing, to consider our respective parts in the program until about two weeks ago. It was immediately apparent to us, as I hope it will be later to you also, that it would be unprofitable for us to enter upon a joint discussion of the same surgical measures, as the printed announcements of the meeting seemed to promise. For in the first place there were so many operations deserving of mention that time would not permit both of us to comment on them; and in the second place we found that with respect to certain of the newer surgical procedures neither of us had any personal experience. This meant that we would have based our comments on the same published reports, and we would inevitably have said so nearly the same things that the result would have been painful both to the audience and the speakers. We therefore decided to divide the various procedures between us largely on the basis of personal experience or familiarity with them. And one unexpected result of this division of the topics is that I am to discuss with you chiefly those operations upon or in immediate relation to the heart, while Dr. Andrus will concentrate mainly upon surgery of the larger blood vessels, a field of great and increasing importance.

With this brief word of explanation, I should like to plunge at once into a consideration of two recent surgical measures designed to increase the blood supply of the heart.

The first of these is intimately associated with the name of Claude Beck of Cleveland. It has long been recognized that great diminution of the blood flow through the coronary arteries, resulting from sclerosis and narrowing of these vessels, is responsible for the majority of disability and deaths that are properly charged against heart disease. It is clear therefore that any measure which would augment the blood supply of a heart that is failing because of inadequate nutrition would be of the greatest possible value. After years of experimental work upon dogs, Beck was convinced that this purpose could be accomplished by attaching other tissues directly to the surface of the heart. In animals he employed pericardium, pericardial fat, omentum, and muscle; in man, a portion of the pectoral muscle only. He believed that blood vessels would grow from the healthy pectoral muscle into the anemic myocardium and would supply the heart with enough additional blood to improve its function. He performed the first such operation upon a human being in February 1935, and the last one apparently

about three years later.

From the last published report of Beck in November 1937 a few facts may be briefly summarized. At that time twenty-five patients with advanced anginal heart failure had been subjected to the operation; nine of these had died and sixteen were living. Eight of the nine deaths occurred within a week after operation. The operative mortality was 50 per cent in the first twelve patients, but only 15 per cent in the following thirteen. Of the sixteen surviving patients, thirteen had been followed for five or more months after operation; three were thought to have shown great improvement, nine moderate improvement, and one slight improvement. The statement is made that "there were no patients who were not improved by the operation." At this time Beck recognized and frankly stated that the beneficial effects of the operation might be explained by any of several possibilities. One was an actual increase in the blood supply of the heart due to new vessels from the muscle graft; a second was a redistribution of blood in the coronary arterial system caused by opening up of intercoronary communications by trauma to the epicardial surface of the heart; and a third was the interruption of nerve pathways from the heart, which might prevent pain impulses from reaching the central nervous system.

Now on the basis of this report, one must admit that there was considerable ground for encouragement. An operative mortality of 15 per cent is certainly not excessive when one considers the serious condition of these patients before operation, and it is probable that further experience would have reduced this to a still lower figure. Of the thirteen patients observed for five or more months, twelve, or 92 per cent, are said to have shown moderate or great improvement. Why then did Beck cease performing the operation when the future appeared so promising? I am not certain that I can state all the reasons, but some of them seem to be fairly clear.

In the first place, I think there was growing uncertainty in the mind of Beck and his medical colleague Feil as to whether the muscle grafts were in fact providing the myocardium with a new supply of blood, or whether the early improvement might not be due to some other cause. Autopsies upon experimental animals had demonstrated the existence of vessels passing between the graft and the myocardium, but these were few in number and for the most part microscopic in size;

there was serious question as to whether these minute channels could convey enough blood to be of any real value. Furthermore, the mere demonstration that such vessels existed did not prove that the blood flow was from the graft into the myocardium; it was equally conceivable that it was in the reverse direction. Then it was not possible wholly to ignore the criticisms of experienced and thoughtful surgeons to the effect that the method of performing the operation materially lessened its chances of success, because the pectoral muscle, having been deprived of its nerve supply and having been placed at complete rest, must inevitably atrophy and therefore suffer a diminution in its own blood supply. Moreover, there was the demonstration by Burchell that much of the experimental work upon which the human operation was based contained a serious fallacy and did not justify the conclusions that had been drawn from it. I shall discuss this work of Burchell more fully in a moment, since it applies equally to the next operation. And finally, as Beck himself has stated, he was convinced that the value of the procedure must be determined ultimately by one thing only, namely, its demonstrable effects upon human cases, rather than by animal experiments or theoretical considerations. Having performed the operation upon some thirty patients, he decided that this was a group large enough to warrant at least tentative conclusions if the survivors could be carefully observed for some years or until the time of death.

Before stating briefly my own estimate of the operation, I should like to discuss another that is quite similar and designed for the same purpose. It consists of the attachment of a portion of the omentum, instead of the pectoral muscle, to the heart. This operation, known as cardio-omentopexy, was apparently first performed by Laurence O'Shaughnessy of London, who was tragically killed during the war in Flanders last June. Briefly, it consists of opening the pericardium and placing upon the epicardial surface of the heart a suitable portion of omentum brought from the abdomen through an opening in the diaphragm. Apparently O'Shaughnessy started his experimental work upon dogs before Beck had published any of his comparable observations, and the work of the two men has many striking similarities. They were both led to the conclusion that the heart could be abundantly supplied with blood from an outside source. In selecting the omentum as the new source of blood, O'Shaughnessy was influenced by the fact that one of the known functions of this tissue is to supply blood to other organs

that need it, and he stated that it was in fact the only tissue that has this function. In some instances the arteries that have grown from the omentum into other organs have been shown to increase greatly in size, whereas the vessels of the pectoral muscle graft, as already indicated, must be expected to grow smaller.

In the report by O'Shaughnessy and his colleagues in January 1938, it is stated that of the fifteen patients with anginal heart failure subjected to this operation, five had died, one on the operating table, and the remaining four, two to three months after operation. Of the ten who survived, eight became entirely free of anginal pain, and seven of these had returned to active work.

The sad events of the past seventeen months in Europe, and especially the tragic death of O'Shaughnessy, prevent our asking why the operation has not been continued in England, but one may ask why it has not been performed in this country. I have been unable to find a report of such an operation upon a human patient. Before attempting to answer this question I must ask you to go back with me and consider for a moment the experimental evidence upon which Beck and O'Shaughnessy relied. In general it was quite similar, and consisted essentially of the demonstration that it was possible to reduce the coronary blood flow greatly in dogs by constriction or ligation of coronary branches, and yet have the animal survive, provided a collateral circulation was previously established by the creation of external adhesions. Beck and Tichy, in their most successful experiment, estimated that approximately 85 per cent of the total cross sectional area of the main coronary arteries was occluded, yet the animal lived and was normally active. Complete occlusion of single main arteries or partial occlusion of several main stems was effected with survival of the animals, and this result was ascribed to the establishment of a collateral vascular bed by previous operations. O'Shaughnessy laid emphasis especially upon the ability of dogs to perform strenuous exercise some months after ligation of a main coronary artery, provided cardio-omentopexy had also been performed. The demonstration that greyhounds could race normally after such operations was interpreted as indicating that the omental graft had effectively counterbalanced the loss of a major coronary artery. It is true that both observers also secured some evidence of growth of vessels between the graft and the heart, but in most instances this seemed unconvincing or of such lim-

ited extent as to be unimportant. In general the evidence was indirect, and was interpreted, without adequate control, as indicating that the grafts did in fact supply the heart with a considerable quantity of blood.

And now I come to the observations of Burchell, to which I alluded a moment ago. He reëxamined the entire question from the beginning and found a good deal of discrepancy in the reports of different observers upon the immediate and ultimate results of ligation of coronary arteries in the healthy dog, but it is of great interest, and quite relevant to the point now under consideration, that a number of operators prior to Beck and O'Shaughnessy had been able to ligate main arteries with a very low or quite moderate mortality rate. Burchell performed a series of ingenious experiments which resulted in marked constriction of coronary arteries or gradual complete closure of main arteries, in addition to sudden complete closure by ligation. He found that constricting collars with an internal diameter of 1.5 to 2.5 mm. could be placed on all three main coronaries in two operations about two weeks apart, and the animals subsequently showed no disability and could exercise on a sloping treadmill as well as normal animals. When he used a method that resulted in gradual complete occlusion of the vessel, he found that all three main arteries could be closed in successive stages without the production of infarction and without any impairment of the normal cardiac function. He also showed that if dogs survived the immediate effects of ligation of main coronary arteries, there was little or no evidence of cardiac disability after the healing of the infarct. Most surprising of all, he observed that in some instances dogs could survive acute ligation of all three main coronary arteries in successive operations if these were not tied too close to the point of origin, and one such dog seemed to be capable of normal physical activity subsequently. It was possible to prove that in such instances the hearts were nourished through the main coronary stems. You will understand, of course, that all these experiments were performed upon dogs that had not been subjected to any of the procedures employed by Beck and O'Shaughnessy; there was no question of a collateral circulation established by means of previous operation.

Having shown that all the results mentioned by Beck and O'Shaughnessy, as well as others far more spectacular, could be obtained in normal dogs without the use of grafts or pericardial adhesions, Burchell next examined the efficacy of tissue grafts as carriers of blood

into the myocardium. He attached grafts of pectoral muscle or of omentum to the heart in the manner described by his predecessors, and was unable to demonstrate that they exerted any beneficial effect in preventing infarction of the ventricle after ligation of the anterior descending coronary artery. In most instances the thin layer of scar tissues between the graft and the myocardium contained blood vessels that could be seen only with the aid of a microscope. When the tissues were injected with india ink, this thin intervening layer usually appeared clear and avascular, even when the graft and the myocardium were heavily loaded with ink. It was observed that omental grafts formed adhesions to the heart that were very easily separated, and if no injury had been done to the epicardium, adhesions were often completely absent. There was no evidence of increase in vascularization with progressive coronary occlusion, as O'Shaughnessy had assumed there might be, and in only one instance was it possible to demonstrate barium in the coronary vessels after this substance was injected into the omental graft.

He was unable to demonstrate that the vessels seen in the adhesions carried any significant volume of blood. By means of heart-lung preparations he calculated in two animals that the total volume was ½ to 2 cc. per minute, while in two others where occlusion of all three arteries had been effected, no flow through the adhesions could be demonstrated, although the grafts had been in place from 9 to 20 months.

And lastly, Burchell performed the crucial experiment that both Beck and O'Shaughnessy omitted. In three dogs muscle grafts and in three, omental grafts were placed upon the heart, and occlusion of the three main coronary arteries was produced. The animals survived and were normally active. You will recall that it was evidence of this type, although far less convincing and extensive, which led Beck and O'Shaughnessy to conclude that in these circumstances the heart was deriving its blood supply from the graft. But they did not perform the logical experiment that would have proved decisive. Burchell did. He cut the grafts from the hearts in all six animals. You will probably not be surprised when I tell you that the animals were not inconvenienced by removal of the graft, that their ability to work on the treadmill was not impaired, and that there were no electrocardiographic changes to indicate a diminution of blood flow to the myocardium.

I think one must conclude that unless these observations of Burchell

are shown to be inaccurate, which seems to me unlikely, they remove every particle of *experimental* justification for the muscle graft and omental graft operations. But this does not necessarily prove that the operations are devoid of value in human cases, and we must consider briefly what results have been secured so far as this can be determined from available reports. You will recall that in Beck's last published report the statement was made that there was no patient who was not improved by the operation. But as I heard Beck present this material in New Haven, with details and case reports, it seemed to me that only three had shown sufficient improvement to justify a procedure that was attended by an operative mortality of at least 15 per cent. At the time these three had apparently shown considerable improvement, but in the light of our present knowledge the benefit cannot be ascribed without considerable hesitation to an increase in myocardial blood flow due to the graft, and may well have been due to interruption of nerve pathways or to a redistribution of blood in the coronary arterial system. Within the past few weeks Beck has stated frankly that he does not know if the operation has value. Of the patients who survived, only three have subsequently died after periods long enough to make observations upon them of value. Autopsy in one case apparently confirmed the clinical impression that little if any benefit had been derived from the procedure; there was no anatomical evidence that the graft had provided the heart with additional blood. A second patient had apparently been helped by operation, and autopsy showed about a dozen very fine, hair-like vessels running between the graft and the heart muscle. When barium was injected into the coronary vessels, it emerged from the vessels of the graft, but the cleared specimen showed only very minute channels. The clinical result in this case is said to have been far better than would have been expected on the basis of the anatomical findings at autopsy. Beck suggests that for the present the group be regarded as one subjected to a purely experimental procedure, rather than to one of known therapeutic value. If there seems to be some lack of harmony between these later conservative statements and the earlier estimates of therapeutic benefit, it is at least greatly to his credit that he has been willing to alter his views in accord with accumulating experience.

This is perhaps as far as we can go in stating the known facts, for there have been no later reports upon the patients subjected to omentopexy. What then shall we say as to the value of these operations and

their place in future cardiac therapy? Recognizing that our information is still incomplete, it nevertheless seems to me most unlikely that either of them will ever be resumed. I think it is improbable that the improvement in the surviving patients was due to any significant increase in the blood supply of the heart, and if this purpose was not in fact achieved, the operation loses all justification. If some improvement occurred as an indirect result of the procedure, further observations are necessary to determine the mechanism of this and to ascertain if equal or greater improvement cannot be secured from a simpler operation attended by little or no mortality. We may surely wait for the final report upon the patients still living before pronouncing a final verdict, but I do not believe the available information warrants great optimism. The evidence that I have mentioned at some length seems to me clearly opposed to the belief that a valuable therapeutic procedure has been discovered.

I turn now for a few moments to a more recent operation, namely, ligation of the patent ductus arteriosus. As most of you know, the ductus is a vessel of variable size which runs from the aorta to the pulmonary artery, is a vital part of the circulation in the fetus but ceases to serve any useful function after birth and normally closes and atrophies within the first few months of life. When it remains open, it constitutes in essence an arteriovenous fistula through which relatively enormous quantities of blood pass from the aorta into the pulmonary artery because of the much higher pressure in the former vessel, and this leak is continuous through systole and diastole. The blood from the aorta, having been shunted into the pulmonary artery, flows into the lungs, then back to the left ventricle from which it was pumped only an instant before. If the duct is a fairly large one, only a small portion of the left ventricular output is available for the peripheral circulation, which is consequently partially starved.

These mechanical aspects readily explain several of the more important clinical findings associated with the condition. The pulmonary artery becomes moderately or greatly dilated, and there is considerable engorgement of the pulmonary vascular bed because of the tremendous increase in the volume of blood now flowing to the lungs. If the leak from the aorta is of considerable magnitude, it results in the classical signs of aortic regurgitation, namely, a low diastolic pressure, a wide pulse pressure, Duroziez' sign, and usually enlargement of the left ventricle. Some idea of the amount of increased work thrown upon the left

ventricle in cases of large shunts may be obtained from the studies of Eppinger, Gross and Burwell upon some of the patients subjected to operation. They found, for example, that in one patient the peripheral blood flow per minute was approximately 6 liters, while the pulmonary blood flow was more than 25 liters! The volume of blood flowing through the duct was 19.5 liters, or 77 per cent of all the blood entering the pulmonary circulation! In general, they state that from 45 to 75 per cent of the blood leaving the left ventricle passes through the ductus into the lungs, then immediately back into the left ventricle, without having accomplished its normal function of delivering oxygen to the body's tissues. It is not surprising, in view of these figures, to learn that a number of patients with patent ductus are undernourished, and it is easy to understand why many of them die of heart failure induced by the enormous strain thrown upon the left ventricle.

Please do not misunderstand me as implying that all patients who have a patent ductus must inevitably suffer from malnutrition, cardiac enlargement, or heart failure. It is probable that these are invariable manifestations of a large shunt of blood from the aorta to the pulmonary artery, but there would appear to be at least a moderate number of patients who live for many years in perfect comfort with a small open ductus which imposes but little additional work upon the left ventricle. Even in this relatively fortunate group, however, there is a serious and ever-present menace to health: the danger of subacute bacterial endocarditis, which is known to occur in a certain percentage of people with this congenital anomaly.

The possible harmful effects of patency of the ductus, then, consist of malnutrition and underdevelopment of the child, the occurrence of congestive heart failure, and the development of subacute bacterial endocarditis or endarteritis. In the present state of our knowledge it is admittedly impossible to present any accurate figures as to the incidence of patency of the ductus in the general population, or as to the frequency of these complications. Statistics drawn from previous medical literature are worthless for at least two reasons: they represent a strictly selected group, and they include large numbers of infants. The inclusion of infants complicates the figures because the diagnosis of patent ductus is highly uncertain in the first months of life, because it is still unknown how long it may remain patent normally, and because bacterial endocarditis occurs rarely if at all in infancy. Figures as to the incidence of

patent ductus in large groups of autopsies are of doubtful value because there is general agreement that this anomaly is very readily overlooked in routine postmortem examinations; it often requires the most careful search to demonstrate its presence, and it seems probable that it occurs in a higher proportion of cases than has been thought in the past. I am in full agreement with those recent writers who have stated emphatically that no reliance should be placed upon conclusions drawn from such a group as that of the late Dr. Abbott, for the reasons just stated; I refer specifically to this group because it has been quoted in almost every paper written on this subject in the past two years.

Now inasmuch as the three dreaded complications of this condition are all due to the presence of an abnormal channel, it has long been recognized that they might be prevented by the mechanical closure of this duct. The first attempt to ligate an open duct was made, unsuccessfully, in 1937, and it remained for Robert Gross of Boston to perform the first successful closure in a human being, in August 1938. Within a short time he had performed the operation successfully, and with great benefit, upon others, and it was not long before surgeons in other cities were following his example. I have made no attempt to compile a complete list of the operations performed up to the present time, but I can tell you that on January 13, when I had a very happy and profitable meeting with Gross, Burwell, and Eppinger in Boston, Gross had operated upon twelve uninfected cases and one complicated by subacute bacterial endocarditis. There had been only one postoperative death, and that was caused by a Staphylococcus aureus infection. Bullock, Jones, and Dolley of Los Angeles have reported thirteen cases; there was only one postoperative death in their group, and that also was due to Staphylococcus aureus infection. A letter received yesterday from Dr. Bullock informs me that their group now comprises sixteen cases, and there have been no other postoperative deaths. George Humphreys of this city has very kindly provided me with full details of four patients upon whom he has operated at the Babies Hospital, a fifth one operated upon by John Sullivan at Bellevue, and a sixth one (the only adult) subjected to operation by Dr. Blakemore at Presbyterian Hospital. Emile Holman of San Francisco writes me that he has operated upon only one patient with patency of the ductus, and Alfred Blalock of Nashville has ligated the duct in one patient with bacterial endocarditis and one without this complication. Arthur Touroff of New York has operated upon four

patients who were known to have bacterial endocarditis at the time of operation, and I shall have a word to say about these in a moment. There are probably many others operated upon but not yet reported, but these form a group sufficiently large to justify certain comments.

I think it is worthy of emphasis that the operative and postoperative mortality has been extremely low in the uninfected cases. The mortality in the small group in this city is still zero, while in the larger groups of Boston and Los Angeles there have been only two postoperative deaths, both of them from a type of infection that might have occurred after any surgical procedure, and therefore not to be regarded as a specific argument against closure of the ductus.

Those who advocate the operation do so for three reasons. They believe that it will correct malnutrition when this is present, that it will prevent heart failure, and that it *may* prevent the development of bacterial endocarditis. In the cases thus far reported there has apparently been remarkable improvement after operation with respect to nutrition and also with respect to the signs of cardiac enlargement and of heart failure. I may add that theoretically there is every reason to believe that the operation stands upon unassailable ground with respect to these two indications. But when we consider the effect of the operation upon the possibility of subsequent bacterial endocarditis, we immediately enter the field of speculation. We have no proof as yet, and in the nature of the case cannot secure such proof for years, that successful closure of the duct will prevent the subsequent occurrence of a Streptococcus viridans infection in the wall of the aorta or the pulmonary artery where the duct formerly existed. Theoretically, there is reason for believing that unless the operation is done in early childhood, the changes in the pulmonary artery may have progressed so far that this complication may occur even if the duct is closed surgically. To say that no operated case has thus far developed bacterial endarteritis is irrelevant, for it is known that this infection may develop late in life, and we shall have to wait some years before we can speak with confidence of this particular aspect.

But in this connection a special word should be said about the group operated upon by Dr. Touroff of this city. He has courageously attempted to close the duct surgically in four patients who were known to have bacterial endarteritis already; the families and medical advisers of the patients elected this desperate measure because of the hopeless outlook. His first patient has apparently been completely cured of the infec-

tion by ligation and division of the duct; a second one was not helped by closure of the duct, and the other two died of operative complications, which are almost insuperable in the presence of an infection of long standing. I think Touroff deserves our congratulations upon his courage and skill; in extending them, I wish also to express my warm thanks for his kindness in giving me so generously of his time and thoughts when we discussed his cases several weeks ago. I should like to add that in my opinion the almost absolute certainty that death will occur from the infection in these patients is sufficient to justify the admittedly hazardous operation. The fact that it has been successful in one of the two surviving patients in Touroff's group may prove to be highly significant.

At the present moment, then, I think we may safely say that surgical ligation of the duct is indicated in those patients who have enlargement of the heart, and those with imminent or actual heart failure. If there is distinct enlargement of the ventricle and this increases under observation, it is highly probable that heart failure will soon appear. Malnutrition by itself is almost certainly not an indication, since this is associated with a large shunt, which would lead to ventricular enlargement.

One word of caution seems to me not only permissible, but also essential. It is perhaps natural and inevitable that a wave of enthusiasm should sweep the country when a new and promising therapeutic procedure is introduced. Sometimes the enthusiasm is so great as to abolish critical judgment temporarily, and the procedure is applied without proper discrimination to many patients for whom it is unnecessary or actually contraindicated. Already we are being asked to arrange for this operation upon patients who have signs of patent ductus but no evidence of disability, cardiac enlargement, or heart failure. If we knew that such patients would almost certainly develop bacterial endarteritis without the operation and could be promised immunity after the operation, and if, furthermore, the operative mortality remains extremely low, then the procedure would be indicated. But we do not know this as yet. Shapiro of Minneapolis has observed nineteen patients with patent ductus, some of them as long as 17 years, and none has developed heart failure or bacterial endocarditis; Stroud of Philadelphia has observed ten such patients in the past 20 years, and none has developed either of these complications. It is perfectly possible that a majority of these twenty-nine patients may yet die of heart failure or streptococcus infections, but we have no justification as yet for assuming this.

I would not for one moment state or imply that Gross' achievement in perfecting this operation is anything less than his admirers have proclaimed it to be, but perhaps it is my duty to remind you that the great chorus of praise and adulation that has been raised in his honor has a strange resemblance—to my ears at least—to that raised in honor of certain other surgeons within the past fifteen years, whose marvellous contributions have now been forgotten and abandoned. It is my own belief that this operation stands upon a firmer foundation than any of these others; on the basis of our present rather slight knowledge, I believe it will occupy an important place in the treatment of a condition hitherto not accessible to therapy, but I think its ultimate place may be a smaller one, from a numerical standpoint, than certain others now appear to believe. The operation seems to me a noteworthy achievement, of great value in a rather limited group.

The three operations just discussed are so recent that, as I have indicated, it is impossible at this moment to express any final judgment upon their real value and their ultimate place in the therapy of heart disease. In the time that remains I should like to speak briefly of a group of operations which may be appraised with greater confidence because they are of less recent development. Of these there are four that seem deserving of comment.

The first is total thyroidectomy, an operation proposed a few years ago for the relief of anginal or congestive heart failure. Those who sponsored the procedure stated—and I express their statements in a very general way—that heart failure might be ascribed to a discrepancy between the demands of the body and the ability of the heart to meet those demands. If the usual therapeutic measures did not abolish this discrepancy by improving the heart's functional ability, they thought it possible that lowering the demands of the body, by decreasing the basal metabolic rate, might do so. The results of the operation in the early cases seemed quite promising, although many observers refused to accept it because of certain discordant results and because the physiological foundation for the procedure was by no means clear or convincing. I think one may say now in all fairness that the operation has been almost completely abandoned, even by those who introduced it and were most enthusiastic several years ago. Blumgart believes that it is of value in occasional patients whose heart failure is progressive despite all other therapeutic measures, and Geoffrey Bourne of England has reported

highly satisfactory results in a small group of anginal patients within the past few months. I doubt if the reported results justify the scornful rejection with which it has met, but on the other hand I seriously doubt if it will ever come into general use, and I think its value is slight.

A second operation performed upon structures outside the heart in the hope of relieving symptoms of heart failure consists of the injection of alcohol into the upper thoracic sympathetic ganglia. Many of you are aware that the nerve fibers which convey pain impulses from the heart into the central nervous system appear to converge in the upper four sympathetic ganglia, whence they are conveyed across the communicant rami into the posterior nerve roots and the spinal cord. All such impulses may therefore be interrupted if these nerve structures are sectioned or blocked by the injection of alcohol into them. The surgical resection of the posterior nerve roots is a difficult operation, attended by an excessive mortality rate, so injection of alcohol is preferable. If the alcohol is placed accurately in or immediately adjacent to the ganglia, the results are highly satisfactory, and anginal pain is completely or almost completely relieved in from 70 to 90 per cent of the patients. It is very seldom necessary to repeat the procedure because of regeneration of nerves; in some cases the relief has continued without change for a number of years. The operation is a relatively simple one, performed under local anesthesia, and there is practically no operative mortality, but unfortunately its success depends upon long experience and constant practice, so there are very few surgeons who are competent to perform it satisfactorily. This procedure is associated chiefly with the name of James White of Boston, whose series is much the largest in the country. His results have been little short of spectacular, when one considers that he has selected for operation only those patients who have advanced anginal failure and whose lives are almost insupportable despite the best possible medical treatment. I can testify that some of my patients upon whom White has performed this operation have been transformed from complete invalids into normally active individuals free from pain. The only serious objection to the procedure is the occurrence of alcoholic neuritis of the intercostal nerves in a majority of the patients. This may be quite distressing and often lasts for some weeks, but it eventually subsides, leaving normal cutaneous sensation. Despite this real disadvantage, it seems to me this is far the most useful of the surgical measures available for the treatment of those anginal patients who no longer re-

spond satisfactorily to medical therapy. In my opinion it is vastly superior to total thyroidectomy for this purpose.

Lastly I wish to speak very briefly of two operations relating to the pericardium. The first is that sometimes known as the Brauer operation, or by the unfortunate term "cardiolysis," and consists of the removal of portions of the ribs overlying the heart, usually of the 3d, 4th, 5th, and 6th ribs on the left. The operation was originally suggested because of the belief that if the two layers of the pericardium are adherent, and in addition the external layer is densely adherent to the ribs, sternum, and mediastinal structures, the work of the ventricles will be enormously increased because they must in these circumstances pull inward upon a dense, rigid cage at each contraction. Inasmuch as section of the adhesions was thought to be difficult and unsatisfactory, it was proposed to remove the bony attachment of these adhesions, and thus permit the heart to tug upon a soft yielding flap of muscle and skin, instead of bone. The underlying conception has been vigorously assailed in recent years by Beck, who insists that external adhesions of the type just described are not of importance, do not cause cardiac enlargement or heart failure, and are not an indication for operation. There are some, perhaps many, who agree with him, but I am not yet ready to number myself among them. Such experienced observers as Evarts Graham, Bigger, and Blalock have indicated that in their opinion the operation may stand upon a firm basis, although perhaps in a smaller number of cases than was believed a few years ago, and a number of authentic cases have been reported in which dramatic relief of heart failure followed the resection of adhesions or the removal of ribs over the heart. I have myself witnessed such conspicuous improvement in a few patients that I am quite unwilling to subscribe to the view that the operation is valueless. It is quite possible, however, that in some cases the improvement may be due, not to a lessening of the heart's work, but rather to having afforded a large heart more adequate space in which to work. It is my belief that the operation is of great and proven value in a small group of cases.

And lastly I wish to refer to the operation known as pericardiectomy, performed for the relief of signs and symptoms known collectively as the Pick syndrome. These include, among the more important: high venous pressure, low arterial pressure, ascites, a heart that is normal in size or smaller than normal, and usually absence of signs of heart disease. This syndrome is now known to be due to constriction of the

heart by a dense pericardium, which may be extensively calcified or otherwise thickened. The heart is so densely held by this constricting envelope as to be unable to dilate and fill normally in diastole.

The surgical treatment is clearly indicated by this brief description, and consists of the removal of the pericardial scar in whole or in part. When this is successfully performed, the results are most gratifying. Inasmuch as the heart itself is seldom diseased, the removal of its mechanical handicap restores it to normal function, and there is usually a rapid disappearance of the signs and symptoms just mentioned. A large number of patients have been subjected to the operation, the major groups having been reported from the New York Hospital, from Boston, Cleveland, and Nashville. A few minutes ago, at the dinner preceding this meeting, Bernard Oppenheimer told me that he and his associates (Hitzig and Neuhof) have just reported a group of eight patients with this condition upon whom operation has been performed. Five of them showed marked improvement or complete recovery, the periods of observation extending from several months to eight years. Three died, two of them within a week of operation and the other many months later of carcinoma. I am sure Dr. Oppenheimer will not object to my mentioning these patients inasmuch as his report upon them is already in press. Of all the operations upon the heart or pericardium, this seems to me the most important in its results, and perhaps the greatest contribution that surgery has yet made to this field. I hope that Dr. Andrus will tell us of his own experiences with it.

One final word by way of summary and I shall be through. Of the operations mentioned, I believe that those designed to provide the heart with a new source of blood are probably valueless. Surgical ligation of the patent ductus arteriosus seems destined to be of immense importance in a group of patients that will probably always be numerically small. Total thyroidectomy may have a limited place, but in the absence of an elevated basal metabolic rate the indications for it are not very clear and the results are apt to be unsatisfactory. Alcohol injections into the thoracic sympathetic ganglia have been proven highly satisfactory by years of experience. The Brauer operation for adhesive mediastino-pericarditis seems to me of demonstrated value in a few cases, and I think the time has not come to discard it. And pericardiectomy for constrictive pericarditis may be confidently regarded as a major therapeutic procedure and a brilliant surgical contribution.

MORPHOLOGICAL AND FUNCTIONAL ALTERATIONS OF THE CORONARY CIRCULATION

Harvey Lecture, April 18, 1940

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PROBLEMS for investigation which have their origin in the clinic frequently lead the investigator far afield in the course of his search for suitable methods for their solution. Interesting side trips into pathology, physiology or chemistry may result when he is forced to use the methods or seek the help of his colleagues in these subjects. And so it is with the work concerning which I have the honor to speak to you this evening. It had its origin in the clinic and has been carried on during the past ten years in the Department of Medicine of the Lakeside Hospital and Western Reserve University. In the various stages of the work I have had the privilege of having with me a number of younger collaborators, and we have sought and obtained aid frequently from our colleagues, particularly in physiology, chemistry, and pathology. The final result, therefore, may be said to be the product of all of these.

The coronary vascular tree, which supplies blood to the heart, is—with its various ramifications and anastomoses—one of the most complex vascular systems in the body. For this reason, it seems wise to begin with a description of the structure of the coronary circuit and its numerous component parts.

When Galen[1] first applied the name "coronary" to the larger arteries of the heart he was in doubt, apparently, as to whether there was one or two such vessels, and the confused conception which he held concerning their function is brought out by his suggestion that the arteries ended as nerves. It was not until the great publication of William Harvey[2] that the first clear statement of their function appeared. In his *De Motu Cordis*, Harvey states that the heart has a supply of blood for its own especial behoof, in its coronary veins and arteries—". . . hic locus autem cor est; cum solum ex omnibus partibus (non solum in vena &

arteria coronali privato usui) sed in cavitatibus suis tanquam in cisternis, & promptuario (auriculis scilicet & ventriculus) publico usui, sanguinem continet: . . ."

The coronary vessels are shown in the anatomical drawings of Leonardo da Vinci, but it was not until the work of Richard Lower[3] in 1671 that more accurate data concerning the arteries and veins of the heart began to appear. Lower was the first to describe anastomoses of the branches of the arteries, which he demonstrated by showing that liquid which he injected into one artery escaped from the other. Friederic Ruysch[4] in 1704 introduced the corrosion method of studying blood vessels and showed the distribution of their branches. Almost simultaneously Raymond Vieussens,[5] in 1706 and 1715, published the results of his brilliant studies on the heart. His beautiful dissections of single branches of the coronary arteries revealed the distribution of the vessels in the various muscle layers. Of greater significance, however, was his discovery of a new group of blood channels in the heart wall. While opening human hearts at necropsy, he observed that the blood clots, so frequently seen in the heart chambers, had attached to them little tendrils which ran into small openings in the heart walls. Being convinced that these openings were connected with the coronary circuit, he injected saffron into the coronary arteries and observed its escape through the small openings into the auricles and ventricles. Two years later, in 1708, Adam Christian Thebesius[6] demonstrated a connection between the coronary veins and the openings in the heart walls. His experiment —simple and convincing—consisted of blowing air into the coronary veins, with the heart immersed in water, and observing the bubbles of air escape through the openings in the heart wall. Since then these vessels have been known as Thebesian veins, but, as will be shown presently, Vieussens and Thebesius, though unaware of it, were dealing with different groups of vessels which were separated by the capillaries.

In 1798, Abernethy[7] confirmed the results of Vieussens, and, while he did not fully appreciate the significance of his findings, his experiments demonstrated vascular communications between the chambers of the heart and the arterial side of the coronary circuit.

These interesting discoveries were lost sight of, and until the past score of years they have been ignored in almost all anatomical and physiological studies of the coronary system. Recently Kretz[8] and more particularly Crainicianu[9] began to recognize their importance. The latter

showed for the first time that the aggregate diameter of the luminal vessels was almost equal to that of the coronary arteries.

In 1928,[10] when we perfused the coronary arteries and collected the outflow from the coronary sinus and the chambers of the heart, we were astonished to find that approximately 80 per cent of the fluid escaped from the luminal vessels and only 20 per cent from the coronary sinus. It was natural, then, to ask ourselves what role these vessels might play in the circulation of the heart and what relationship they might bear to the arteries, capillaries, and veins. In work with S. R. Mettier in 1928 it was found that if a solution of celloidin too thick to penetrate capillaries was introduced into the coronary arteries some of it escaped by way of the luminal vessels into the chambers of the heart. In another experiment the ventricular chambers were filled with a solution of red celloidin. Suction applied at the ostia of the coronary arteries drew the celloidin into the openings of the luminal vessels. Blue celloidin was then injected into the coronary arteries where it fused with the red. When the muscle was digested off, casts of the arterial luminal vessels were revealed.

These vessels were also demonstrated by wax reconstruction. One of the openings of the luminal vessels in the ventricular wall from which the celloidin protruded was selected under the dissecting microscope and marked with India ink. The muscle containing this vessel was then cut into serial histological sections. Study and wax reconstruction of these sections, in collaboration with T. G. Klumpp and L. J. Zschiesche,[11] revealed two types of vessels which connected the arterial side of the coronary circuit with the heart chambers; one direct from the arterioles, and the other through the myocardial sinusoids directly into the chambers. The more direct arterio-luminal vessels are not numerous, but the arterio-sinusoidal vessels occur in large numbers and are easily recognized. Their structure, except for the irregularity of the lumen, is identical with that of the capillaries. It is quite possible, therefore, that the metabolic exchange through their walls is the same as that which occurs through the capillary walls.

The Thebesian veins are connecting channels between the capillaries and coronary veins on the one hand and the heart chambers on the other. This was shown in our laboratory in 1928, and the excellent work of Grant[12] has demonstrated the various branchings and communications of these veins.

Of the remaining larger branches of the coronary arteries the extracardiac vessels are worthy of note. First described by Albrecht von Haller in 1803,[13] these vessels leave the heart around the root of the aorta and around the ostia of the superior and inferior venae cavae, and in the intervascular pericardial reflections. In work with C. L. Hudson and A. R. Moritz, 1932,[14] they were shown to anastomose with the arteries supplying the aortic wall, the pericardium, the upper and lower surfaces of the diaphragm, the pleural surfaces of the lungs, the trachea and esophagus.

The capillaries of the myocardium are very difficult to recognize; indeed, in the ordinary histological section only an occasional capillary can be identified. In order to visualize the capillary bed, injection of dyes through the coronary arteries or veins must be resorted to. In the dead heart, however, the luminal vessels offer less resistance to the injection mass than do the capillaries; consequently, in most instances attemps to inject the capillaries via the coronary arteries fail, and the mass escapes into the heart cavities through the luminal vessels. Attempts to fill the capillaries through the coronary veins likewise fail because the mass escapes through the Thebesian veins. We found, in 1928,[10] that if a heart can be revived by perfusing it with an oxygenated Locke-Rosenheim solution, the capillaries can be injected without difficulty by adding dye to the perfusate.

With the capillary bed visible it was an easy matter to trace its connections not only with the arterioles and venules, but with the sinusoids and Thebesian veins as well. As a result of these observations it is now possible to construct a diagram of the coronary circulation.

The coronary arteries, as shown in Figure 1, may communicate with extracardiac arteries, with ventricles through the arterio-luminal and arterio-sinusoidal vessels, and finally with one another. If there be any doubt of the existence of communications between the different trunks of these arteries, the preparations of Spalteholz[15] and Gross[16] should dispel it, for in the anatomical sense, at least, these workers have shown that the coronaries are not end arteries. Moreover, even in the event of complete closure of the ostia of the coronary arteries the heart still has access to a blood supply at arterial pressure levels through the extracardiac and arterio-luminal vessels. Two cases reported with Timothy Leary,[17] in 1930, show that the heart is capable of sustaining an active life with the mouths of both coronary arteries occluded. Since reporting

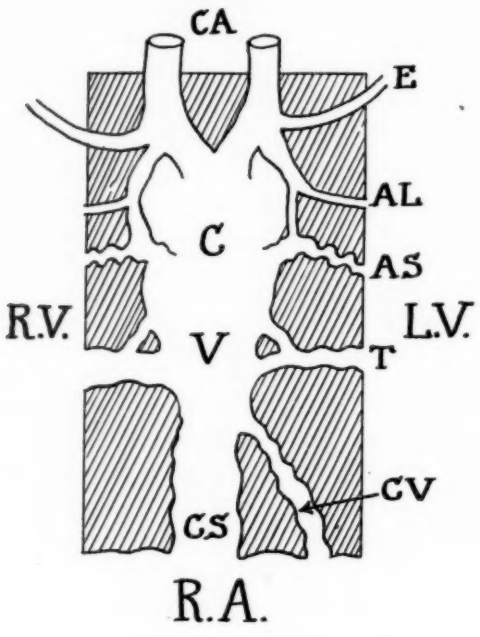

Fig. 1

CA—coronary arteries.
E—extracardiac branches.
AL—arterio-luminal vessels.
AS—arterio-sinusoidal vessels.
C—capillaries.
T—Thebesian veins.
V—coronary veins.
CV— " "
CS—coronary sinus.
R.V.—right ventricle.
R.A.—right auricle.
L.V.—left ventricle.

these cases, a number of others with occlusions of one or both coronary arteries have been recorded. Despite the occlusion of whole arteries, infarction of these hearts did not occur.

The question naturally arises as to how these hearts get their blood supply. In the event of occlusion of the ostia of both coronary arteries one can only conclude that the arterial blood must come either from the extracardiac vessels or from the arterio-luminal vessels. But I know of no evidence that would indicate whether one or both of these sources are utilized. No other channels of sufficient size to supply enough blood to maintain normal heart action are known to exist.

In the event of the closure of the ostium or of a large branch of one

coronary artery, Schlesinger[18] has shown that, if given sufficient time, anastomoses will develop from other branches of the artery. The work of Mautz and Beck[19] on dog hearts would indicate that in these animals closure of one coronary artery results in marked enlargement of the already existing anastomoses. In their experiments a large branch of one artery was tied off in gradual stages. This gave sufficient time for the collateral anastomoses to develop. Supportive evidence is also found at autopsy, in instances where syphilitic aortitis or advanced coronary sclerosis may completely occlude one or both major branches of the coronary arteries without the production of infarction. One important factor should be pointed out at this time, and that is the factor of time. All of these processes require weeks, if not months or years, to bring about the gradual closure of the main trunks of the arteries, thus giving ample time for the existing anastomotic channels to begin to function.

The role that the luminal and Thebesian vessels play in the circulation of the normal heart has received very little attention. Evans and Starling,[20] Markwalder and Starling,[21] Anrep and Hausler, 1928,[22] and others have shown that part of the blood entering the coronary arteries does not return through the coronary sinus, and they have assumed, with Thebesius, that the luminal vessels serve only as auxiliary veins. These workers, unfortunately, did not observe pressures within the chambers of the heart, nor did their studies take into consideration the possibility of an ebb and flow of blood in the luminal vessels. The flow from the luminal vessels, under the conditions of their experiments, was constant at about 40 per cent of the coronary artery inflow.

Stella[23] found no flow from the peripheral ends when he cut the coronary arteries. His animals lived for two minutes at most after the arteries were cut, and the hearts failed instantly, so allowance must be made for the fact that these experiments were made on moribund animals.

Bohning, Jochim and Katz[24] injected killed cultures of staphylococci and hay bacilli and other particulate matter into the vena cava, under conditions which precluded entrance of the injected material into the coronary arteries. They found the bacilli in the capillaries of the heart wall, and concluded that the luminal vessels act as a source of blood supply in normal hearts.

Recently, Wiggers[25] has approached the question of the direction of flow of blood in the luminal and extracardiac vessels from a theoreti-

cal standpoint, taking into account the pressure relations and the pressure gradients available for flow through anastomotic channels, if they exist.

Under normal conditions, the pressure gradients are such that a transfer of blood from the coronary arteries to the left ventricle could occur during the whole of diastole and during the early part of isometric contraction. In the right ventricle and auricles, on the other hand, the pressure gradients are such that a theoretical transfer of blood could occur throughout systole and diastole.

The practically identical pressures in the coronary arteries and extracardiac anastomoses would prevent any flow of blood between them at any time in the cardiac cycle.

If one examines the pressure relations that exist when the coronary ostia are occluded, as shown in the curves of Wiggers,[26] it is obvious that the pressure gradients are ideal for flow from the ventricle into the luminal vessels and sinusoids, but the answer to this question must await experiments not yet complete.

During the past two years, with Doctors D. E. Gregg, R. W. Eckstein, and J. T. Roberts, work* has been carried on in our laboratory with the purpose of finding out the direction of the flow in the luminal vessels in the right ventricle and the effect upon the flow of changing pressures within that chamber. By means of a shunting device with a two-way valve introduced into the pulmonary artery of a dog it was possible to allow the blood entering the pulmonary artery to flow through the device directly into the pulmonary arteries, as usual, or, by turning a cock, to shunt the blood from the right ventricle into a rubber balloon which, as it filled, displaced an equal volume of blood from the flask outside the balloon back into the pulmonary artery. In this manner Chicago blue or India ink was introduced into the right ventricle without the possibility of its reaching the lungs or the coronary arteries. During the experiment right and left ventricular pressures were recorded.

After introduction of the shunting device the pressures were allowed to become constant, with the blood flowing directly through the pulmonary artery. The usual pressures were about 100/7 in the left ventricle, and 19/2 in the right ventricle. Blood was then shunted into the balloon and India ink was introduced into the vena cava at such rate that

* This work, and the metabolic studies reported later in this paper, were made possible by a grant from the Commonwealth Fund.

the right ventricular pressure was not changed. At the desired time the heart was stopped by the introduction of KCl or glacial acetic acid into the left ventricle. It was then fixed, sectioned, and examined microscopically for the presence of India ink in the vessels of the myocardium.

These experiments gave convincing evidence that the pressure gradient between the right and left ventricles determined the direction of flow in the luminal vessels of the right ventricle. So long as the pressure in the left ventricle was greater than that in the right, no significant flow took place from the ventricle into the luminal vessels. There was an occasional superficial vessel in the septum that contained ink, but these extended less than 2 mm. below the endocardial surface. The capillary bed, by gross and microscopic examination, was free from injection mass.

If, at the time of injection of the ink, the right ventricular pressure was greater than the left, a very significant flow took place from the ventricle into the luminal vessels, as evidenced by a complete injection of the capillaries and larger vessels. When the capillaries were filled with ink the heart was grossly black, and this observation was utilized in a third experiment. In the beginning, with the left ventricular pressure definitely higher than the right, an injection of ink into the vena cava was begun. The heart remained red in gross appearance—evidence that the ink was not entering the myocardial vessels from the ventricle. The pressure relations were then changed by raising the right ventricular pressure and lowering that in the left ventricle simultaneously. As the pressures became equal the ink began to enter the luminal vessels and the heart turned black the instant that the right ventricular pressure exceeded that of the left. Inasmuch as these observations were made in the intact animal, the conclusion is drawn that there is no flow of blood from the right ventricle into the luminal vessels, under normal conditions.

Support is given to these results by the following experiments in rabbits. If Chicago blue is injected into the right ventricle of a normally beating heart at a pressure insufficient to raise the right ventricular pressure to that of the left ventricle the heart turns blue only after the dye has passed through the lungs and entered the myocardial capillaries via the coronary arteries. If, after injection of the dye into the right ventricle, the heart is allowed to beat two or three times and at this point the right ventricular wall is suddenly opened with a pair of scissors near the pulmonary artery, the right ventricular pressure drops to zero and

the dye never reaches the left ventricle. Microscopic examination reveals no dye in the myocardial vessels.

The normal function of the luminal vessels in the left ventricle is unknown.

Capillary Bed

The normal relationship of the capillaries to the muscle fibres which they supply with blood is of considerable importance. They communicate freely, not only with arterioles and venules, but equally with all the luminal connections. Thus, the muscle fibres enjoy several possible sources of blood supply. It has long been known that at the time of birth the muscle fibres are small in diameter. During physiological growth the fibres increase in diameter and length, thus increasing the thickness of the heart wall, the capacity of its chambers, and the total heart weight. There are also concomitant changes in the blood vessels of the heart. Ehrich, de la Chapelle and Cohn,[27] for instance, found that the arteries of each ventricle increase in direct proportion to the weight of the ventricles.

The muscle fibres, the capillary bed and the quantitative relationship between the two were studied in our laboratory during growth, in rabbits and in man, in 1937, in collaboration with R. A. and L. J. Shipley,[28] and during the past three years in human hearts, with J. T. Roberts.

Certain precautions are necessary in studying quantitative changes in muscle fibres and capillaries. First, a method of fixation and mounting the histological sections must be used which will avoid the errors that result from shrinkage. Secondly, accurate determination of the number of capillaries depends upon complete injection of the capillary bed in the section of tissue studied. In our hands, this has been uniformly successful only in those hearts which were revived and injected while beating. In only a few instances have successful injections been made by other methods in hearts obtained more than six hours postmortem.

At the time of birth, in the rabbit heart, there was one capillary for every five or six muscle fibres. The capillaries were evenly distributed and ran parallel to and alongside the fibres. In the human heart the same relationship was observed. In the heart of a seven months' fetus there was one capillary to six muscle fibres, while in the heart of an infant three weeks old, the ratio was four fibres to each capillary.

With the increase in diameter of the muscle fibres as a result of

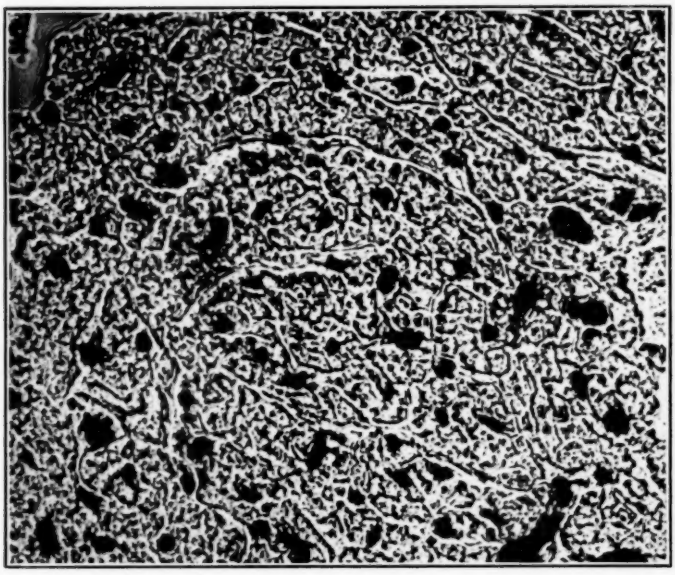

Fig. 2—Heart of infant (3 wks.). Note small fibres.

growth, the fibre-capillary relationship began to change, so that in the heart of a child sixteen years of age there was one capillary for two muscle fibres. This change in the ratio of fibres to capillaries continued until growth was completed, at which time the ratio of fibres to capillaries was approximately 1:1. We have relatively few observations on the hearts of growing rabbits and of children, with no children's hearts between the ages of one and eight years, but, as will be seen in Figures 4 and 5, the curve of the fibre-capillary ratio in the human heart is almost identical with that in the rabbit heart. Moreover, this curve seems to take the form of a hyperbole, which is a form frequently observed in growth phenomena.

Once growth is completed, the fibre-capillary ratio remains constant, at approximately 1:1, so long as the heart remains normal, both in man and in the rabbit.

In a group of twenty-six normal hearts of adults the fibre-capillary ratio ranged from 0.97 to 1.68, with an average of 1.34 ($\pm$0.023). The remarkable uniformity of this figure throughout the group is in sharp

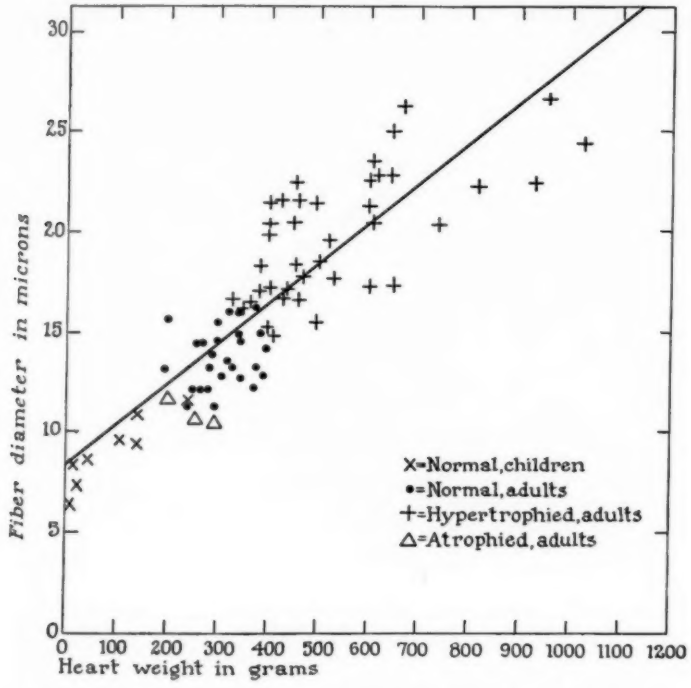

Fig. 3—The influence of growth, hypertrophy and atrophy on fibre diameter.

contrast to the constantly changing one during growth.

It has been claimed by Tangl[29] that the increase in fibre diameter during growth may be as much as six-fold. Our observations show an increase in human hearts during growth of five-fold. Findings in the rabbits were of the same order. Thus, the one capillary which at birth supplied five muscle fibres, in the adult supplies one fibre, the area of which is approximately that of five fibres at birth.

In view of the increasing mass of muscle and the changes in the fibre-capillary ratio during growth, it is interesting to observe the effect of this change upon the concentration of capillaries in a square millimeter of heart muscle. In the human heart at birth there were approximately 4000 capillaries per square millimeter. This concentration remained essentially the same in children's hearts throughout the period of growth, the average for all children's hearts being 3700. The same constancy was

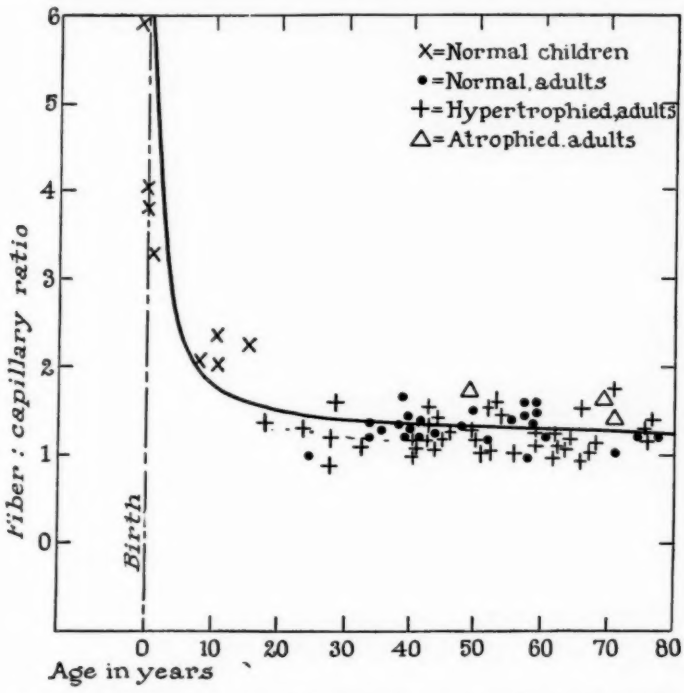

Fig. 4—The influence of growth, hypertrophy and atrophy on the number of fibres per capillary.

found in the concentration of capillaries in the rabbit hearts.

The changes occurring during growth of the heart may be summarized as follows: At birth there are five muscle fibres to each capillary. As the fibres increase in size the fibre-capillary ratio changes constantly until there is approximately one capillary for each muscle fibre. Throughout the growth period the concentration of capillaries per unit of area is maintained at a constant level. It is obvious, therefore, that the increase in muscle mass is accompanied by a corresponding increase in the total number of capillaries.

In the normal hearts of adults the capillary concentration also remains remarkably constant. In the twenty-six hearts with an age range from twenty-five to seventy-seven years, the number of capillaries per square millimeter ranged from 3000 to 4000, with a mean of 3342 ($\pm$36). The standard deviation for the entire group was only eight

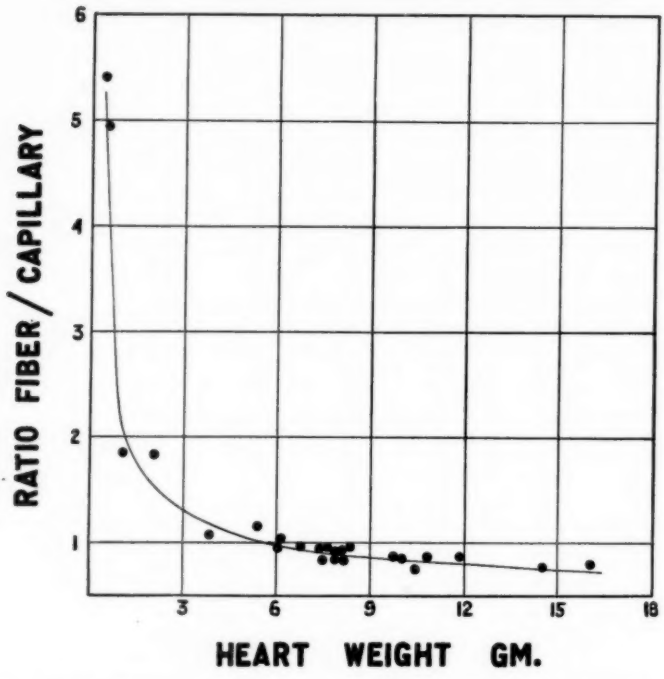

Fig. 5—The influence of growth upon the fibre-capillary ratio in rabbits (after Shipley, Shipley and Wearn). Reproduced by courtesy of the *Journal of Experimental Medicine.*

per cent and, when one considers the wide age distribution for the group, the capillary concentration is obviously fairly constant throughout adult life, so long as the heart remains normal.

The muscle fibres in the hearts of normal adults also remain fairly uniform in size, with a mean diameter for the group of fourteen micra.

We then undertook to find out if any changes occur in the muscle-capillary relationship during cardiac hypertrophy. Indeed, it was this question which prompted this work in 1923. It became necessary to establish the normal relationships described above before we could proceed with the problem of hypertrophy.

The frequent finding at necropsy of an hypertrophied heart that has failed is familiar to all. Other than the hypertrophy, the muscle of these hearts often shows no abnormalities. Why, then, should an enlarged muscle without demonstrable abnormality fail? Hypertrophy is fre-

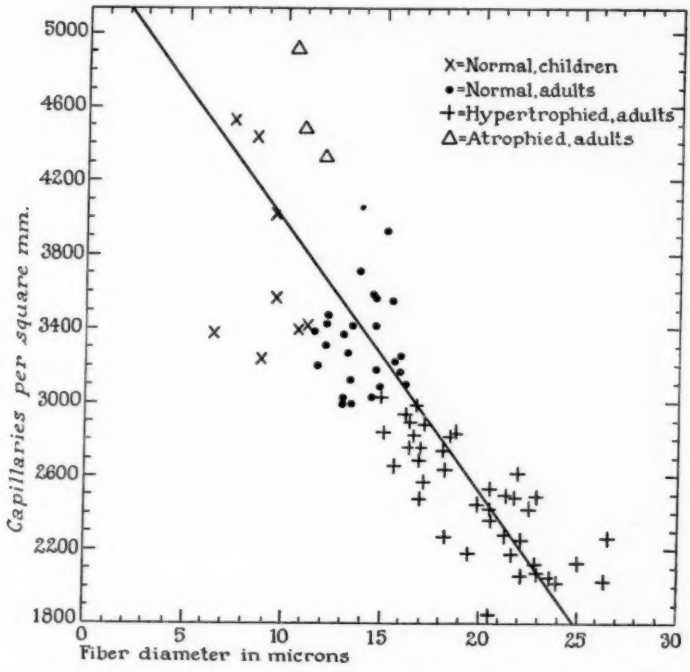

Fig. 6—The influence of fiber diameter on the capillary concentration.

quently spoken of as being compensatory. On the other hand, it is also considered to be one of the most dependable signs of heart damage. There is no factual evidence, so far as I can learn, to support the claim that an enlarged heart is a more efficient performer. It occurred to us that the enlargement of the heart might result in a diminution of blood vessels in the heart wall. The exact problem may be stated in this way: Is it possible that during the enlargement of the muscle, the capillaries do not increase proportionately? If this should prove to be true, hypertrophy would result in an actual decrease in the concentration of capillaries per unit of tissue.

In order to answer this question, observations similar to those carried out on growing hearts were made on a group of hypertrophied hearts. There was clinical and pathological evidence of disease in all of these hearts. Hypertension, rheumatic fever, syphilis, and coronary sclerosis were frequently present. Death was the result of congestive failure in

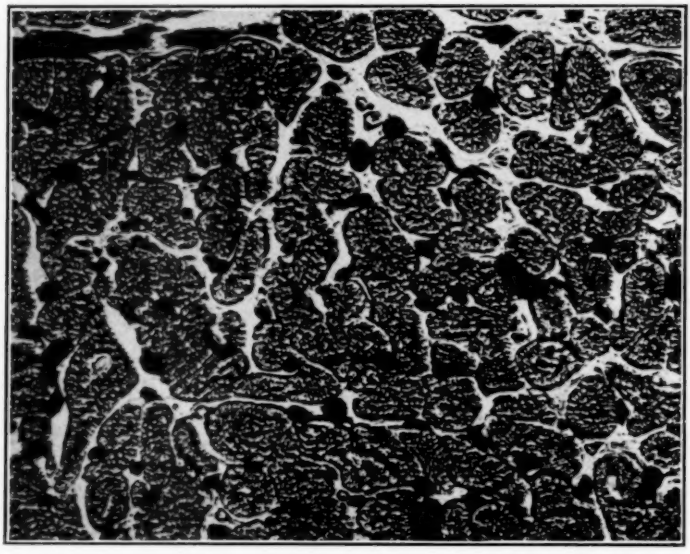

Fig. 7—H 30. Wt. 300 gm. Capillaries 3551 per sq. mm. Fiber diam. 15.5 micra.

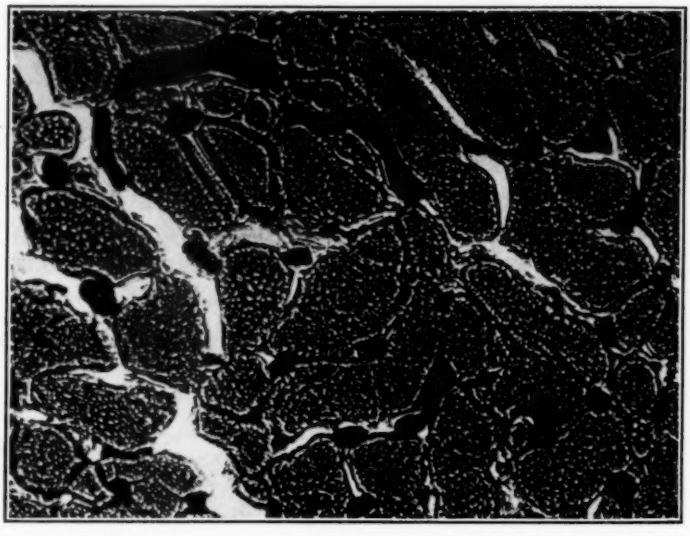

Fig. 8—H 52. Wt. 930 gm. Capillaries 2251 per sq. mm. Fiber diam. 22.1 micra.

the majority of these patients.

The degree of hypertrophy varied considerably. Some of the hearts showed so little enlargement that they might well have fallen within the normal group. At the other extreme was a heart weighing 1150 gm. The average weight for the group was approximately 525 gm. (±16.1).

During hypertrophy the muscle fibres increased in size throughout the heart. The enlargement was in almost direct proportion to the increase in weight of the heart. In many instances some of the fibres reached diameters triple those of normal heart fibres.

Despite the marked increase in size of the fibres, the fibre-capillary ratio showed practically no change. The ratio of approximately 1:1 was as uniform in this group as in the normal hearts.

The most striking change found during hypertrophy was observed in the concentration of capillaries in the muscle. As the muscle fibers increased in diameter the capillaries were pushed farther apart, and this resulted in a decrease in the concentration of the capillaries per unit area of muscle. The concentration of the capillaries diminished in proportion to the increase in the fibre diameter and to the increase in heart weight. Thus, the larger the heart, the less the concentration of capillaries.

With these data concerning growth and hypertrophy in hand it becomes clear that they are separate and distinct processes. Growth of heart muscle is accompanied by a proportional increase in the number of capillaries, while hypertrophy of the muscle results in an actual decrease in concentration of capillaries. It would avoid a great deal of confusion if we reserve the term "hypertrophy," as applied to hearts, to those that show changes in keeping with this definition. The much discussed increase in size of the hearts of young athletes is frequently spoken of as hypertrophy. But whether it is actually hypertrophy or growth can be settled when such hearts are subjected to the type of study just described.

Atrophied Hearts

Three hearts, atrophied as a result of wasting disease, were studied. The muscle fibre diameter decreased and the capillaries moved more closely together, resulting in an increase in the capillary concentration.

In all quantitative measurements of muscle and capillary-muscle relationship which have been described up to this point our observations

TABLE I

	AV. HEART WT.	MEAN AGE	AV. HT. WT. BODY WT. RATIO	AV. FIBRE DIAM.	AV. NUMBER CAPILL. PER SQ. MM.	AV. FIB./CAP. RATIO
	gm.			*mu*		
Child*	20	3 wk.	0.0069	7.4	4513	4.04
Normal adult	310	51	0.0054	13.9	3342	1.34
Hypertrophy	535	49	0.0088	19.8	2483	1.23
Atrophy	247	66	0.0043	11.1	4613	1.69

* Single heart for comparison.

were confined to muscle bundles of myocardium in order to obtain an accurate picture of the functioning muscle. Recently, we have studied some of these hearts in a different manner. The same measurements were made, but instead of confining the observations to muscle bundles, cross sections of the whole heart tissue were studied so as to include scars, large fibrous septa lying between muscle bundles, etc. A comparison of these results with those obtained from the study of the muscle revealed in some instances some interesting results.

In the hypertrophied hearts the inclusion of counts on the whole tissue caused a marked drop in the total capillary concentration, sometimes to less than half that in the muscle bundles.

Microscopical studies of the scarred areas in the hypertrophied hearts showed a marked disturbance of the muscle-capillary relationship. Muscle fibres were frequently partially or completely surrounded by scar tissue, and fibres in various stages of degeneration were found. The important point, from our viewpoint, was the fact that many of these fibres were without capillaries. In many fields, also, the capillaries were fairly evenly distributed in the scar tissue where the fibres had completely disappeared.

It is obvious that the efficiency of fibres without capillaries and of capillaries without fibres in performing their respective functions might be seriously interfered with.

With the guidance and help of Professor J. R. Musselman of the Department of Mathematics of Western Reserve University we have studied the data of the quantitative relationship of the capillaries to the muscle mass. It was found that a high order of correlation exists—so

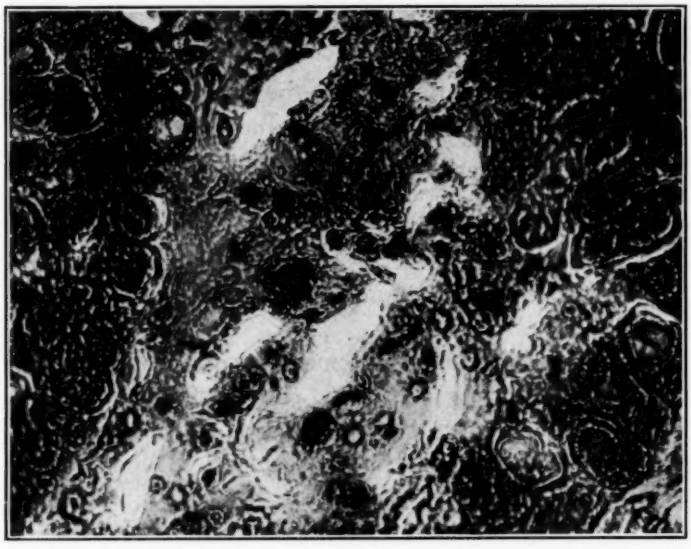

Fig. 9—Scar in myocardium (rheumatic fever) showing distribution of capillaries.

high at times that it suggests the possibility of a governing biological law. There is, for instance, a practically perfect positive correlation between the heart weight and the average muscle-fibre diameter. Thus, if the heart weight is known, the average muscle-fibre diameter can be calculated with a probable error for the predicted value of ± 1.435 mu.

Likewise, between the average fibre diameter and the number of capillaries per sq. mm. there is a close correlation and, if the fibre diameter is known, the capillary concentration can be calculated with a probable error for the predicted value of ± 209 capillaries.

As a result of these two correlations, the expected correlation between the heart weight and the capillary concentration was found to exist, so that, given the heart weight, the capillary concentration can be calculated.

And, in similar manner, the fibre-capillary ratio can be predicted from the patient's age.

One can also calculate the capillary surface area available for the diffusion of oxygen and the exchange of metabolites in a cubic centimeter of muscle. This was found to be:

Hearts of children	1145	sq. cm.
Adults (normal)	1184	" "
Hypertrophied	623	" "

When this ratio is plotted against the heart weights (Chart V), the hearts of children and normal adults show the same wide range, without apparent correlation to heart weight. The hypertrophied hearts fall well below the range of the normal hearts and show a definite rectilinear negative correlation of high degree with the heart weight. This we interpret as showing that, in the normal hearts of children or adults, the capillary surface per cubic centimeter of muscle is constant and independent of heart weight.

At this point the temptation to speculate is almost irresistible. Our observations on the changes during hypertrophy show that, as the heart enlarges, the distance from the capillary wall to the periphery of the muscle mass which it supplies becomes greater. This means that the route over which oxygen has to diffuse and metabolic products have to travel increases in proportion to the degree of hypertrophy. Moreover, the actual capillary surface available for exchange is markedly decreased per cubic centimeter of muscle. It seems safe to say that at some stage in the course of hypertrophy a point will be reached where metabolic exchange will be seriously interfered with.

Chemical studies designed to find out whether hypertrophy interferes with the exchange of metabolites are not yet sufficiently advanced to answer this question, but a few observations have been completed and are perhaps deserving of brief mention.

The oxygen utilization by the heart muscle has, in the past, been studied, for the most part, either in isolated hearts or heart-lung preparations. Katz and Long[30] have shown that skeletal muscle can establish an appreciable oxygen debt without harm, whereas heart muscle in the same animal can tolerate very little oxygen debt. Indeed, any appreciable diminution in the oxygen in the arterial blood reflects itself immediately in the weakening of the heart beat.

Oxygen, of course, is required for the removal of lactic acid, and it was shown by these workers, as well as by others, that the heart tolerates only about one-quarter of the lactic acid concentration that skeletal muscle does. The heart, therefore, is dependent upon its contemporary oxygen supply in order to function efficiently.

Hastings and Blumgart[31] have recently found that brief periods of

TABLE II

Coronary arterial-venous oxygen difference in dogs

OXYGEN CAPACITY	OXYGEN CONTENT					
	Arterial		Coronary vein		Femoral vein	
vols. %	*vols. %*	*% sat.*	*vols. %*	*% sat.*	*vols. %*	*% sat.*
15.1	12.7	84	2.6	18	12.3	82
17.6	16.1	92	3.1	18	12.8	73
18.1	17.6	97	9.8	53	13.3	74
20.7	20.2	98	5.0	24	15.3	74
19.8	18.8	95	6.2	31	13.1	66
15.5	12.5	81	3.6	23	7.8	50
23.1	21.0	90	3.7	16	15.7	67
21.8	19.1	88	2.8	12		
21.2	18.1	85	2.6	12		
22.1	17.2	79	3.3	15		
23.5	20.5	88	3.7	16		

anoxemia produce measurable chemical changes in heart muscle, in the absence of histological change.

In work now in progress with J. W. Price and D. E. Gregg, the oxygen utilization of the normal heart is being determined in the dog. With the animal anesthetized and, therefore, at complete rest, blood samples have been collected under proper conditions and as nearly simultaneously as possible, from the left ventricle, the coronary sinus, and in some instances from the femoral vein.

The percentage saturation of oxygen in the venous blood from the coronary sinus was constantly and surprisingly low. The figures ranged from 12 per cent to 53 per cent, with an average of 23 per cent, whereas the average saturation of the femoral venous blood was 70 per cent.

The following experiment illustrates the methods used. The heart was exposed under sodium pentobarbital anesthesia with artificial respiration. In some instances the chest was closed and made air tight by means of the pericardium, which was sewed to the walls to form a cradle in which the heart could beat outside the chest. This procedure also enabled the animal to breathe normally. Care was exercised to avoid tension on the vessels and nerves at the base of the heart. Each set of three blood samples was taken within a period of five minutes. The following results from one experiment are typical:

DATE	CORONARY VEIN			RIGHT VENTRICLE			LEFT VENTRICLE		
	O_2 content	O_2 capacity	Saturation	O_2 content	O_2 capacity	Saturation	O_2 content	O_2 capacity	Saturation
	vols. %	*vols. %*	%	*vols. %*	*vols. %*	%	*vols. %*	*vols. %*	%
2/15/40	4.6	21.8	21	14.8	21.7	68	21.3	21.8	98

TABLE III

Percentage O_2 saturation

	ARTERIAL	VENOUS	
Himwich & Castle.....	92–108 av. 99	12–64 av. 38	Gastrocnemius, exercised
Barcroft & Kato.....		51–70	"
Price, Gregg & Wearn....	79–97	12–53 av. 23	Heart anesthetized dog

Oxygen capacity was determined on each blood sample and each percentage saturation value was calculated from corresponding content and capacity values.

Barcroft and Kato, in 1915,[32] and Himwich and Castle,[33] in 1927, determined the O_2 utilization in the resting and exercised leg muscles of dogs. A comparison of their findings with ours is shown in Table III.

From these figures it is obvious that percentage saturation of the venous blood of the heart of a dog at rest is significantly lower than the venous blood from exercised skeletal muscles. The heart, in what might be called a resting state, therefore, leaves very little oxygen in the coronary venous blood.

This almost complete use of available oxygen by the normal heart offers a plausible explanation for the findings of Katz and Long that the heart will not tolerate an oxygen debt. It also suggests that any increase in work by the heart must be met by an increase in the coronary blood flow, which could be brought about either by the opening of additional capillaries or by an increase in the velocity of the flow of blood in those capillaries already open.

In regard to the opening of additional capillaries it may be said that in numerous experiments in our laboratory we have never been able to demonstrate an intermittence of flow in the capillary bed of the myocardium, nor has any convincing evidence of intermittence ever been published, of which I am aware. Our work is still in progress, but it seems very likely that the heart uses all of its capillaries at all times. The mechanism available, therefore, for meeting strain is most probably an increase in blood flow in the coronary circuit.

It is now generally accepted that the muscle pigment also plays a role in oxygen transfer and storage. Whipple[34] and his co-workers[35] have shown that myoglobin, or muscle hemoglobin, is present in the myocardium of puppies to the extent of 100–200 mg. per 100 gm. of muscle, increases to 300 mg. at puberty, and reaches 300–400 mg. in adult dogs. They showed that exercise or activity can increase the amount of pigment in the myocardium and the lowest values were encountered in the most inactive animals.

Hurtado et al.[36] observed that dogs kept at high altitudes in the Andes have more myoglobin than dogs kept at sea level. This finding was interpreted as an adaptation to facilitate O_2 exchange in the face of chronic anoxemia.

In view of the increase of myoglobin in heart muscle during normal growth and during the chronic anoxia of high altitudes, we have begun observations upon the muscle hemoglobin in normal and hypertrophied human and rabbit hearts. While our data are too few to justify final conclusions, we have found, thus far, no appreciable difference in the myoglobin content of normal and hypertrophied hearts of rabbits or man. These results are in keeping with those of Cowan and Bauguess,[37] who found no increase in myoglobin in hypertrophied hearts in rats. If these findings prove to be constant they will represent another fundamental difference between the process of hypertrophy and that of normal growth.

Several changes occur in hypertrophy, therefore, which at some stage of the enlargement will impede oxygen diffusion and the exchange of metabolites. At what point during the process of hypertrophy and to what extent they interfere must await further study of the metabolites with a simultaneous measurement of the flow of blood in the coronary arteries.

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EFFORT, TRAUMA, OCCUPATION AND COMPENSATION IN HEART DISEASE*

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BECAUSE of the frequency of heart disease the question of compensation in relation to it has always been an important problem, and it is even more so today as a result of a great increase in the number of workers employed in the national defense program.

For a number of years my colleagues and I have been especially interested in the role of effort, work and trauma in various heart diseases and have collected data on this subject.[1] Tonight I should like to state my conclusions concerning compensability in the main conditions of the heart. I have been seeing compensation cases over a period of ten years but their number forms only a small part of my medical practice. This has enabled me to avoid the error of the man doing only compensation work who tends to think that effort and trauma play a role in every disease and the error of the man who does not interest himself at all in compensation and believes that it offers no problem.

As a physician I am concerned here with the medical aspects of the problem and not with the numerous legal ramifications which may attend individual cases. In each case the following questions should be considered: (1) Was the stated effort, occupation or injury capable of producing the symptoms of the patient or the damage in the heart found on examination? (2) Was heart disease present prior to the strain or accident? The latter may have aggravated a preëxisting heart condition or may have been coincidental. (3) If the strain or injury has damaged the heart, how long will this effect persist? Usually symptoms referable to effort or trauma last a relatively short time, that is, hours, days, weeks or at most several months. If symptoms persist, or appear, later than this, they may be related to the antecedent heart disease, and not to the exertion or injury.

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The problem requires careful consideration and must be approached with an unbiased mind. A good general rule to remember is that the interval between an effort or accident and the onset of symptoms is usually short; the latter are delayed in only a few instances.

In the course of my talk I shall illustrate my point by citing short case reports. I wish to emphasize the fact that I shall purposely omit those in which a relationship to effort or trauma is obvious and readily admitted. I shall quote only those cases referred to me as heart conditions causally related to effort and trauma, but in which I think any association was dubious or not present.

Hypertension and Arteriosclerosis: In spite of the very extensive experimental work performed in the past few years the cause of ordinary high blood pressure or essential hypertension, that is, the type not due to obvious kidney disease, remains obscure. We know that there is a familial tendency and a frequent association with obesity and glandular disturbances. It is a chronic condition which comes on gradually and often without symptoms, and is not compensable. This applies also to enlargement of the heart and hardening or sclerosis of the arteries, both of which result from or accompany high blood pressure. Cardiac enlargement and arteriosclerosis develop over a period of years and cannot be related to any particular event or effort. Incidentally the term "chronic myocarditis," which has been applied loosely to this type of heart disease, should be discarded. Instead one should specify chronic disease of the coronary arteries with scarring or fibrosis of the heart muscle. When high blood pressure and hardening of the arteries have become developed after a number of years, several complications may occur.

"*Stroke*": A "stroke" may be produced in three ways. The commonest is rupture of a small artery in the brain resulting in hemorrhage. Secondly, a clot or thrombosis may form locally in a small blood vessel. Thirdly, a clot may be dislodged from a diseased heart and an embolus may settle in the brain. All three of these result in damage to brain tissue and may be followed by loss of consciousness, paralysis, etc., which may be very brief in duration or may persist. I believe that the third type, namely, dislodgement of a clot from the heart, is probably not related to effort. The relation of cerebral hemorrhage and thrombosis to strain, however, is not definite. The general opinion is that they are due to hardening of the arteries and occur independently of effort, but

some authors hold the opposite view. It is necessary, therefore, to examine each case carefully for evidence of previous high blood pressure and arteriosclerosis. If these have been present the stroke may be merely coincidental to the effort. Trauma to the head, even without fracture of the skull, can produce concussion and contusion of the brain and subdural hemorrhage with neurological signs and symptoms. It must be remembered, however, that, although a stroke may seem to be the result of an accident, actually it may have caused the accident. Thus, a man, R. C., was driving his automobile which crashed. Examination revealed that he had suffered a stroke, presumably caused by the crash. However, several persons driving behind him had noticed that he had slumped in his seat and that the car had swerved repeatedly and in fact was out of control for 1500 feet prior to the accident. It became obvious, therefore, that the stroke had occurred first and had caused the man to lose his ability to drive accurately. The stroke was associated with hardening of the arteries of the brain.

Heart Failure: A second complication of hypertension and arteriosclerosis is heart failure, that is, the heart is unable to maintain a normal blood circulation. It also occurs in other types of heart disease when the heart is badly damaged. The patient has difficulty in breathing, and on examination the lungs may be congested, the liver enlarged and the ankles swollen. Sometimes these are present for long periods without the patient's being aware of them. In fact, he may be able to perform his usual work. As a rule, heart failure is a natural sequence in the progressive course of heart disease. Occasionally, however, acute heart failure sets in following unusual effort or strain. I do not believe that the latter can induce heart failure in a normal heart, but when there has been long-standing heart disease, or when there is acute involvement of the heart, as in rheumatic fever, coronary occlusion and many infections, an unusual exertion may strain the heart sufficiently to result in heart failure. Nevertheless, it is pretty generally admitted now that the commonest exciting factor of heart failure in chronic heart disease is infection and not effort. When heart failure immediately follows strain, it is usually acute, that is, there is sudden congestion of the lungs or pulmonary edema; it is rare to find other evidence of heart failure such as congestion of the liver and swelling of the legs. When these are present it is probable that they existed to some degree prior to the exertion. I may add that the term "acute dilatation" of the heart, used as a diag-

nosis, should be discarded since, if it occurs at all, it is merely one sign of sudden heart failure.

Angina Pectoris Due to Coronary Artery Disease: A third complication of hypertension and arteriosclerosis is angina pectoris. This term is applied to pain over the heart region. There are many causes outside the heart of pain in this location, such as ulcer of the stomach, rheumatism of the spine, neuritis, gall-bladder disease, shingles. In the heart, disease of the valves and inflammation of the aorta, as occurs in syphilis, may produce heart pain, but the usual cause of angina pectoris is hardening or sclerosis of the coronary arteries which supply the heart muscle with blood and enable it to keep on contracting all the time. This condition is apt to occur particularly in persons with high blood pressure. Persons with coronary artery disease may feel pain beneath the breast bone or sternum when they walk or are emotionally upset, because the narrowed arteries are unable to supply the greater blood flow required by the heart under strain. The pain usually lasts only a short time and is relieved by rest or nitroglycerin, a drug which dilates the coronary arteries. There are no after effects of the attack. Therefore, if the first attack of angina pectoris occurs during a patient's occupation immediately following severe exertion, that attack may be compensable for a relatively short time. On the other hand, subsequent attacks of pain should very rarely, if at all, be attributed to the original effort, a view not held by some writers. The attack of pain results from a temporary insufficiency of blood flow through the already diseased coronary arteries and not from any new damage in the artery induced by the effort. Hence, future attacks of pain are associated with the chronic disease of the coronary arteries from which the patient had already suffered. The case of an automobile mechanic, N. A., aged 32, illustrates this point. He developed his first pain over the heart while shoveling sand on a truck. Later several attacks came on at home. The first attack, sustained while shoveling sand, was probably the result of the effort but the later attacks were not, since examination showed that he had had high blood pressure and a very large heart for many years. The natural course of his disease had thus reached the stage when chest pain appeared spontaneously.

The problem is frequently complicated by the fact that the patient denies any symptoms prior to the exertion. For example, a workman, L. A. No. 8504, 53 years old, claimed that he had never had any pain

or illness before lifting a thirty-five pound bolt of cloth, following which he experienced an attack of pain. I saw him three years later and he claimed that since that attack he had felt pain over the heart whenever he exerted himself. In spite of repeated questioning he was firm in his statement that he had never felt any pain prior to the effort described. Yet two physicians testified that he had experienced heart attacks with pain three years and two years before the effort, during one of which he had been in a hospital, and that several confirmatory electrocardiograms had been taken. I too, found on examination that this man had had heart trouble for many years. Therefore, only the attack of pain immediately following the lifting of the bolt of cloth was compensable, and only for a short time; the pain over the heart during the following years, like that prior to the exertion, was associated with his long-standing heart disease and was unrelated to the effort described. This experience is quite a common one not only in my own practice but, I am sure, in that of other physicians.

Coronary Occlusion or Thrombosis: This is THE heart attack, which is characteristic and usually easy to diagnose. It also produces typical changes in the electrocardiogram. It occurs most often between the ages of 50 to 60 years, but one-third the cases are under 50. The great majority of patients have had high blood pressure and angina pectoris due to coronary disease. About three and one-half times as many men as women sustain an attack. The latter is the result of a sudden complete obstruction of one of the coronary arteries by a clot. This cuts off the blood supply to a large area of the heart and death of the affected muscle occurs, a condition called cardiac infarction. It is agreed that a clot does not form in a coronary artery unless that artery is already hardened or diseased.

Effort and Coronary Occlusion: In a series of 1700 attacks of coronary occlusion[2] detailed histories have revealed that the attack was not related to effort, excitement, occupation or other external factors, for it began practically always during sleep, rest or some routine activity. The attack occurred during or directly after unusual strain in only 2 per cent. This is an insignificant figure since all of us exert ourselves at least several times a day and if effort were a factor in precipitating coronary occlusion, the majority of attacks would be associated with exertion. Coronary occlusion would therefore be far more common than it is.

Recently one author[3] has reported two cases in which a heart attack

occurred while playing baseball. One man of 45 stumbled and fell on his buttocks while batting at ball and had the attack. Another man of 43 slipped while playing ball and had the attack as he tried to right himself. The author, in all seriousness, attributed the heart attack in each case to the mishap. Surely if such slight exertion were capable of inducing a heart attack it would be unsafe for any person over 40 or 45 years of age to do much more than remain quiet or at most walk slowly.

Another point against attributing any influence to effort in the onset of coronary occlusion is the fact that in the 1700 cases studied almost 100 of the attacks were sustained by persons who had been in bed for considerable periods suffering from a chronic ailment such as lung abscesses, cancer, heart failure. Certainly the problem of exertion does not arise in this group.

Occupation and Coronary Occlusion: Occupation did not play any role in coronary occlusion for in our series of 1700 cases it occurred in all types of occupation and professions and in all strata of society. Furthermore, we divided our cases into three groups, laborers and workers, storekeepers and business men, and professional persons, and found that the proportion of each of these groups was practically the same as in the general population of New York City.[2] Thus, coronary occlusion is just as apt to occur in the executive sitting behind a desk or even retired as in the longshoreman lifting heavy weights. Obstruction of a coronary artery takes place in the natural course of coronary artery disease, and, as we have shown, is not caused by exertion even if the latter is unusual. Surely it is not related to ordinary activities performed every day. Yet, I have been asked to examine cases in which coronary occlusion was attributed to such routine occupational activities as running an elevator (M. B. 8418); blocking hats (S. S. 7545); working at a small punch press (P. S. 7642); a mail dispatcher (D. S. 7823) lifting a twenty-five pound bag, a common performance in his job; carrying two bundles totaling twenty pounds (A. G.); a milkman (N. S. 9518) walking up a flight of stairs with only four quarts of milk in a container; he had been doing much harder work for twenty years. All of these men had had heart disease for many years and the heart attack or coronary thrombosis was part and parcel of this process, not affected by external factors such as work.

Mechanism of Coronary Occlusion: Our conclusion that effort does not play a role in coronary occlusion is based on clinical data in a very

large series of patients. On the other hand, largely on theoretical grounds, some writers have stated that coronary occlusion can be precipitated by effort. They base this opinion upon recent pathological studies showing that in the natural course of arteriosclerosis, that is hardening of the arteries, hemorrhages form in the lining of the arteries, and that such an intimal hemorrhage in a coronary artery often initiates the formation of a clot or thrombus. Their reasoning is that unusual effort and excitement produce a rise in blood pressure or directly result in the hemorrhages just mentioned. This is purely speculative since there is no evidence at all for it.[4] As a matter of fact, a number of observations point against the validity of such a theory. We have found these hemorrhages just as frequently in persons without elevated blood pressure and in patients who have been bed-ridden for weeks or months, as in persons who have high blood pressure and who exert themselves. Moreover, Winternitz[5] injected fluid into the coronary arteries of men dying from heart disease under the unheard of pressure of 500 to 1000 mm. Hg without producing these blood vessel ruptures. It seems clear that elevation in blood pressure is not the cause of these. It would be no more reasonable to assume that the destruction of red blood cells in the body, which is a natural, physiological process going on all the time, was the result of effort or was influenced by it.

The Premonitory Phase of Coronary Occlusion: In the few bona fide cases in which a heart attack occurred during unusual exertion or excitement the relationship was coincidental. We have calculated that 500,000 attacks of coronary occlusion occur annually[6] and it is natural that a number of them take place during work. It takes time for the occlusion to form[7] and in these patients the final obstruction happens to take place in the course of their work but it is not brought on by it. This concept explains the observation of lesser degrees of pain several days or even weeks prior to the acute attack. During the premonitory stage the patient usually is well enough to continue working, and, if he performs some unusual exertion, he is apt to feel pain or the severity of the occlusion may be increased. But I repeat that the occlusion had already been in the process of formation and its completion is unrelated to effort. We have had the opportunity of observing a number of patients during the premonitory phase and have put them to bed. In spite of this they went on to develop the complete attack after several days or weeks. Thus, S. C. No. 9587, a man of 65, had sustained heart attacks

nine and seven years before, but had been free of pain since then. Several weeks previously he began to complain of frequent chest pain. I saw him after several days and suspected that a coronary occlusion was in the process of formation. Accordingly, I put him to bed, in spite of which he suffered a typical acute heart attack three days later.

In summary, we have shown that coronary occlusion is not produced by effort since it occurs almost always in the absence of unusual strain and just as often in those whose work is very light as in those who do manual labor.

Cardiac Infarction Without Coronary Occlusion. Acute Coronary Insufficiency: At this point I wish to emphasize that I have been speaking of the classical heart attack, that is, coronary occlusion or thrombosis, in which an obstruction forms in one of the coronary arteries and results in destruction of a certain area of heart muscle, a condition termed infarction. The latter can also occur without obstruction of a coronary artery. For example, when the coronary arteries are hardened or sclerotic, they are too narrow to permit an increase of blood to flow through them which is required when the patient exerts himself or becomes excited. As a result of not receiving enough blood and oxygen the muscle becomes necrotic or infarcted. This results in pain and even in death. This condition is called coronary insufficiency with infarction or necrosis of the heart and usually can be distinguished from coronary occlusion or thrombosis with infarction.[8] Unlike the latter it may in certain instances be caused by effort, excitement and trauma and therefore is compensable. I shall cite a case to illustrate coronary insufficiency with necrosis or infarction of the heart muscle, without complete coronary artery obstruction.

M. M., a woman of 72, was attempting to cross a busy thoroughfare but was frightened back to the curb by a passing automobile which did not quite touch her. Soon after reaching the sidewalk she collapsed and by the time an ambulance had arrived she was dead. At necropsy the medical examiner found a severe degree of chronic heart disease but no acute thrombosis. In this case the fright increased the demand of the heart muscle for blood but this could not be supplied. Incidentally, if the automobile had injured the woman, no matter how slightly, the death would have been attributed to trauma. This emphasizes the necessity of exercising great care in compensation cases.

Operation and Coronary Occlusion: Several years ago we drew at-

tention to the fact that an operation, even if minor, may be followed by heart involvement. This is usually due to coronary insufficiency but in some cases it is possible that coronary occlusion is induced by operation. Thus A. M. No. 8706, 39 years old, injured his finger at work and it became infected. After some time it was incised and three nights later he sustained a heart attack. There was no history of heart symptoms at any time prior to the operation and it is possible that the latter was causally related to the attack.

Rheumatic Fever and Chronic Cardiac Valvular Disease: Rheumatic fever is really a disease of the heart. Its cause is unknown but the onset is often associated with a sore throat or cold. The first attack usually occurs in childhood or adolescence and recurrences are very common. Severe effort has been considered by some a competent cause of a recurrence of rheumatic fever but in the cases in which the question of such causal relationship has arisen I have not been convinced of such an association. I may mention the case of a workman S. R. No. 9245, a man of 35, in whom many joints became inflamed following a fall. These seemed to be related until it was discovered that he had come to work limping prior to the fall. It is most likely that the joint inflammation had been present before the injury.

During the acute stage of rheumatic fever there is an acute inflammation of the lining of the heart valves, i.e., endocarditis, and of the heart muscle, that is, myocarditis. In most cases a chronic deformity of the valves, i.e., chronic cardiac valvular disease gradually takes place over a period of months or years, causing leakage through the valves and resulting in enlargement of the heart and murmurs audible to the examiner. All these are progressive changes in the course of rheumatic fever and cannot be ascribed to any external event. If a murmur is discovered following some unusual strain it is almost certain that the murmur antedated the exertion by many months at least, even though the patient was unaware of any trouble in his heart. We have already pointed out that in chronic heart disease heart failure is usually associated with infection. This applies particularly to rheumatic heart disease, but in rare instances heart failure may come on acutely following severe strain.

Syphilitic Heart Disease: Syphilis often results, after a number of years, in deformity of the aortic valve of the heart or in disease of the large artery leaving the heart, namely, the aorta, in which a bulge or

aneurysm may form. These changes are due solely to the syphilitic infection and not to any external factor such as occupation, effort or trauma. The disease of the aorta and aortic valve usually comes on very insidiously and gives rise to symptoms only after the lesion is fully developed. Therefore, when some specific event or effort is more or less coincidental with the onset of symptoms it seems natural to the patient to attribute these to the effort or accident, whereas actually the underlying condition had been present for many years. We have seen that this applies as well to cases of coronary artery and rheumatic heart disease. Although a syphilitic aneurysm of the aorta is not produced by effort or trauma, the question arises whether these may cause rupture of such an aneurysm which is already present. It is possible that severe trauma may do so but I believe that effort does not. My remarks apply as well to aneurysm of the aorta produced by rheumatic fever and arteriosclerosis.

Dissecting Aneurysm of the Aorta: There is another type of aneurysm of the aorta called dissecting aneurysm of the aorta. It is a rare condition that occurs as a result of advanced hardening and degeneration of the medial wall of the aorta, usually in association with high blood pressure. Because of the latter it has been claimed that the process may be initiated by some unusual exertion, or that the latter causes rupture and fatal hemorrhage. I believe, however, that this occurs at rest or during sleep more frequently than during exertion and may be independent of these or other outside influences.

Trauma of the Heart: The heart and large blood vessels definitely may be traumatized as a result of external injury, and, indeed, it is remarkable that the heart is not involved much more commonly, in view of the frequency of accidents. The injury may be direct to the chest or indirect to the abdomen. Also it may or may not penetrate the chest wall. Penetrating instruments such as a knife or dagger may cause a tear in the heart muscle or aorta; with these there is usually blood in the pericardial sac around the heart.

Trauma and Valvular Disease: Not infrequently the question arises whether a murmur in the heart, signifying a damaged valve, has not resulted from a strain or injury. I hardly believe that effort can produce changes in the valve even if it was previously diseased, but trauma of the heart may cause rupture of a valve. Yet this must be a very rare occurrence, indeed. This problem is almost always simplified by the

finding of enlargement of the heart and other murmurs presumably present for a long time, providing that the murmur in question was long-standing. I saw such a case several years ago. A painter, H. G. No. 8979, 39 years old, claimed that he had been entirely well until six months previously when an iron gate weighing 200 pounds became unhinged and hit him in the lower back. He was forced to go home but returned the next day and continued at his regular employment during the next five months, when he found that work was too difficult for him. He was unable to carry a ladder or cans of paint and complained of shortness of breath. On examination I found two murmurs, indicating disease of both the aortic and mitral valves, and the size and configuration of the heart were those associated with a heart condition of many years' standing. This proved that the blow to the patient's back obviously played no role. Only when there is a definite history of injury to the heart and no evidence of previous heart disease may a murmur reasonably be attributed to the accident.

Commotio and Contusio Cordis: A blow against the chest or abdomen may cause either of two conditions: there are functional derangement (commotio) and bruise (contusion) of the heart. In the former there are no actual anatomical changes in the heart, but, as in concussion of the brain, there is a physiological disturbance in the function of the heart resulting chiefly in irregularities in rhythm. In contusion of the heart the impact of the chest wall against the heart is more forceful, resulting in actual damage in the heart muscle, chiefly hemorrhages and lacerations. A favorite accident producing this condition occurs at the steering wheel with pressure against the chest. Such an accident may also rupture the heart and blood vessels. When the heart is bruised, heart failure with congestion of the lungs may set in acutely and result even in death. Occasionally the heart failure advances more gradually and is evidenced by swelling of the liver and legs.

Trauma and Coronary Occlusion: In the literature trauma has sometimes been considered a competent cause of coronary occlusion or thrombosis. However, a detailed study of the subject[2] and the experience of my colleagues and myself have convinced us that trauma never precipitates classic coronary occlusion or thrombosis. The reported cases in which coronary occlusion was attributed to trauma prove on closer study to be actually instances of contusion of the heart muscle and not coronary occlusion. When the latter was present, its relation to trauma

was entirely coincidental. Let me cite a case.

H. G. No. 7698, 46 years old, was feeling tired and out-of-sorts one day when he went to work. While stacking coils one slipped out of his hand and struck the front of his chest. Pain developed after a short time but he continued working for five days. By that time the pain had become severe and he consulted a physician. An electrocardiogram showed that he had sustained a recent coronary occlusion. It was my opinion that the patient had long-standing disease of the coronary arteries and that the occlusion had been forming or had been completed prior to the trauma and actually may have led to the accident. This was indicated by the fact that the man did not feel well before coming to work. Tiredness is a common premonitory symptom in coronary occlusion. In any case, the injury did not produce the occlusion. Cardiac damage may be caused by trauma, but it is due to contusion of the heart and not coronary occlusion. The differentiation can usually be made with the electrocardiogram.[2]

When the heart is injured symptoms usually appear soon after the trauma has been sustained. However, occasionally an attempt is made to link an accident to a heart attack many months later. Thus, F. S. C., a man of 45, suffered a fracture of the skull from which he gradually recovered. Eleven months after the accident he sustained a coronary occlusion which was attributed to the accident, in spite of the long interval and the fact that the man had long-standing heart disease with hypertension.

Trauma and Angina Pectoris Due to Coronary Sclerosis: What has been said of the relation of trauma to coronary occlusion holds to a great extent for angina pectoris due to coronary sclerosis. Contusion of the heart may result in pain in the heart region soon after the accident, which may be repeated during a relatively short period. But repeated attacks of pain or persistent angina pectoris over a period of months or years should not be attributed to injury to the heart except in the rarest cases. Angina pectoris, as we pointed out earlier, is associated with disease of the coronary arteries, a process that takes years to develop. In contusion the heart muscle, and usually not the coronary arteries, is injured and healing takes place after several weeks, with subsidence of symptoms. The following case illustrates the problem. J. A. No. 6927, 46 years old, claimed that he was well until the truck that he was driving turned over and his left hand and arm were injured and his chest bruised.

The laceration of his hand was sutured and he remained in the hospital eight days. Two or three weeks after the accident, he began to notice pain in the chest when he walked. This symptom persisted. Examination showed that he had had elevation of blood pressure and heart disease for some time. This was the basis of his heart pain, further proof of which is afforded by the relatively long period of two or three weeks which elapsed between the accident and the onset of the pain.

Trauma and Bacterial Endocarditis: In rare instances trauma may produce an infection from which the germ may enter the blood stream and result in blood poisoning with infection of the heart valves, that is, an acute malignant endocarditis. This is the only type of endocarditis which is compensable. One common type of infection of the valves, subacute endocarditis, almost always takes place on valves previously diseased, either since birth or after rheumatic fever or syphilis. In most cases the infection is caused by a specific germ, the Streptococcus viridans. Although it is sometimes claimed that this disease may result from injury, there is no proof of this. Indeed, it is very unlikely since the Streptococcus viridans is practically ubiquitous. If an infection with this germ, resulting from trauma, could produce endocarditis the latter would be very common, whereas it occurs relatively infrequently. Furthermore, in hospital and private practice, a history of external abrasion or wound is never obtained in these cases.

Accidents Caused by Heart Disease: In considering trauma one must not forget that a person with heart disease, no matter what the type, may sustain an accident as a result of temporary disability due to the disease. Unless one is careful the accident may erroneously be considered the cause of the heart condition. For example, a man, I. J. G., 60 years old, was driving his automobile and ran into a lamp post. Examination soon after revealed that he had suffered a heart attack. At first this was attributed to the accident. However, several witnesses stated that they had noticed the man slump in his seat prior to the accident. It was probable therefore, that the heart attack had occurred first and, as a result, he had lost control of the wheel. The heart attack was associated with long-standing heart disease.

Cardiac Irregularities: Occasionally an irregularity of the heart rhythm may set in suddenly during heavy work or after unusual strain. The most common serious irregularity is termed *auricular fibrillation.* In this condition the rhythm is completely irregular. It may be transient

or permanent. Usually it is found in patients with heart disease but it may also occur when the heart is not affected organically. If it persists heart failure may ensue. While the irregularity usually sets in without any precipitating factor, it may follow an effort or injury in which case it is compensable even if the heart was abnormal. If the irregularity is transient the period of compensation should end with the cessation of the arhythmia unless it has been severe enough to induce heart failure.

The following case illustrates the difficulty frequently encountered in determining the precipitating cause of auricular fibrillation. H. J., 33 years old, carried a box weighing 25 to 30 pounds from the street floor to the basement when he suddenly developed rapid irregular heart action. He had had five or six similar episodes previously. He smoked thirty cigarettes and drank three cups of coffee daily. Investigation showed that he was suffering from overaction of the thyroid gland, that is, hyperthyroidism or Graves' disease. Several possible causes of the heart irregularity were therefore present. Thus, Graves' disease is often associated with attacks of auricular fibrillation. The latter may also be precipitated by tobacco or coffee in susceptible persons. Finally, the exertion may have induced the attack.

These remarks about auricular fibrillation hold good for another disturbance in rhythm, namely, *paroxysmal tachycardia.* This is a sudden rapid, regular beating of the heart which may last a short time or several days. It is particularly apt to occur in people with normal hearts. *Skipped beats* or *premature beats* may appear following severe exertion or excitement, but they have very little significance. They are exceedingly common and probably occur occasionally in all of us, although most people are not aware of them.

Carbon Monoxide Poisoning: In carbon monoxide poisoning the oxygen in the blood is replaced by the carbon monoxide and the tissues of the body are deprived of oxygen, a condition called anoxemia. As a result, damage is done to the blood vessels and tissues of the body. Although the brain is chiefly affected by the anoxemia the heart muscle may also be involved. If the patient survives the acute stage, this cardiac damage may become chronic and produce such symptoms as heart pain, shortness of breath and even heart failure. However, I am convinced that, as in the case of effort and trauma, carbon monoxide poisoning does not produce classical coronary occlusion or thrombosis. A number of writers have published cases purporting to show a causal relationship

between the two but the evidence has been very uncritical. Often the diagnosis of coronary occlusion has been made when actually merely heart damage is indicated. Most of the claimants were over the age of 45 and therefore probably had had diseased coronary arteries for some time. The following case report[9] is a typical one in which coronary occlusion was attributed to carbon monoxide, but the improbability of any relationship will be obvious. A man, 36 years old, had lived near an oil and gas field and burned unrefined wet gas. He developed an illness characterized by temperature of 103°, stupor, delirium, cold sweat, nausea and vomiting. A diagnosis of coronary thrombosis was made, resulting from the chronic inhalation of carbon monoxide, even though no confirmatory laboratory tests were made. Even if the diagnosis of coronary occlusion is assumed to have been correct, its relation to the gas is purely speculative.

Before one attributes heart disease to carbon monoxide poisoning one should be certain that this has actually occurred and that heart disease had not been present previously. However, it must be remembered that carbon monoxide may aggravate a heart condition.

Effort Syndrome: An interesting and important condition in compensation is effort syndrome or neurocirculatory asthenia or "soldier's heart." Originally described during our Civil War by Dr. DaCosta and studied in detail in the World War, it is also met in civilian life. It occurs in men more frequently than in women, and particularly in thin, asthenic persons in the young adult age group. It is a disturbance or weakness of the nervous control of the heart and circulation, and thus is a functional disorder, that is, there is no organic disease of the heart. In addition to numerous obviously nervous and stomach complaints, heart disease may be simulated by such symptoms as pain over the heart, palpitation and shortness of breath. The chest pain may be quite severe. Furthermore, there may be murmurs and changes in the electrocardiogram. The ability to exercise may be diminished. As a result, these patients often seem incapacitated. However, a careful history and examination usually distinguish this condition from true or organic heart disease. This disorder occurs in persons of constitutionally nervous tendency. These people may go along relatively well for long periods and then break down completely when faced with a specific situation or event. Acute symptoms may be precipitated by an emotional upset, whether it is an accident, a fright, or an unpleasant task, and it is some-

times difficult to exclude these factors as compensable. It is my impression that this disorder is only exceptionally compensable since these people are always on the brink of a precipice and symptoms are apt to appear at almost any time. In one case, E. C., 21 years old, who complained of pain over the heart I discovered that sixty to eighty cigarettes were smoked daily and the pain may have been due to this. A careful history in these cases usually reveals adequate psychological cause for the patient's symptoms.

The Importance of an Accurate History: At this point it will be obvious that in determining compensability following effort or trauma it is essential to obtain a very complete and accurate history. The latter should be taken in great detail and without any prejudice, and should include not only the events connected with the strain or accident but also the previous health of the patient and his subsequent course. In this way a number of facts may be elicited which are relevant to the case. For example, a longshoreman, J. D. No. 9611, suffered a heart attack while working and was quite ill. Upon close questioning, it was discovered that a fellow longshoreman had noticed that he was very sick when he arrived that morning. His physician also told of previous heart disease. Hence, the attack may have occurred before the man went to work. Another case, G. S. No. 6361, was a handy man of 44 who claimed that he had been entirely well until one day he picked up a 75 pound trap while working in a steam room, immediately following which he experienced severe pain in the chest which proved to be a coronary thrombosis. However, his family physician stated that the claimant had had high blood pressure for many years and pain for at least two weeks prior to the strain. Later on the claimant admitted that he had had high blood pressure. Another instructive instance was the case of a brewery truckman who carried numerous kegs of beer up several flights of stairs. As the history was first presented to me, the man was well until he died suddenly an hour later, presumably of coronary occlusion. However, I obtained a detailed history which disclosed the fact that the man had succumbed immediately after the exertion. Although we believe the latter did not precipitate the coronary occlusion, it cannot be denied that it may have contributed to the patient's death.

The history should be obtained in full as soon after the effort or trauma as the condition of the patient permits, and particular attention paid to any possible precipitating incident. I emphasize the importance

of an early history because I have frequently noted that patients brought to a hospital with coronary occlusion gave no history of strain or accident and yet, when the case came up in court at a later date, they testified that their symptoms had followed immediately or soon after some particular event. A comprehensive history elicited at the time of the injury or strain is more valuable than one taken later. This history, considered in the light of the preceding condition of the heart and the disability following the event, should enable one to make a correct and just evaluation of compensation.*

Summary

The relation of effort, occupation and trauma to heart disease frequently offers a difficult problem and each case must be carefully considered.

Symptoms may be due to preëxisting heart disease and the effort or trauma coincidental. Yet effort and trauma may aggravate previous heart disease. Effort does not damage a normal heart.

The effort is significant if it is unusual and not routine, and if symptoms arise immediately or soon after. The latter is also true of trauma.

A "stroke" may occur in the course of hypertension and arteriosclerosis. It is probably not related to effort, but the effect of trauma cannot be excluded.

Heart failure usually is a result of progressive heart disease and may be induced by infection. Only rarely is it precipitated by exertion, but the latter may aggravate it.

Angina pectoris is associated with coronary sclerosis. Individual attacks may be related to effort or trauma but later attacks or a persistent anginal syndrome rarely is.

Effort, occupation and trauma play no role in coronary occlusion. The opposite view is often based on a confusion of coronary occlusion with the syndrome of angina pectoris, coronary insufficiency with cardiac infarction, preliminary pain in coronary occlusion, and contusion of the heart.

Coronary insufficiency usually occurs in association with coronary sclerosis and may be related to effort and trauma.

Rheumatic fever rarely if ever is precipitated by effort or trauma.

Aortic aneurysm due to syphilis or sclerosis is not produced by effort

* I wish to thank Drs. Harry L. Jaffe and Simon Dack for their help and criticism.

or trauma. In rare instances effort or trauma may lead to rupture or to dissecting aneurysm.

Trauma may produce commotio cordis and contusion of the heart. In addition, the heart, large vessels and, in very rare instances, a valve may be ruptured.

Trauma does not produce coronary occlusion and it probably does not lead to a persistent anginal syndrome.

Trauma may be the result, and not the cause, of heart disease.

Subacute bacterial endocarditis is not causally related to trauma with infection, but acute bacterial endocarditis sometimes is.

Cardiac irregularities may be induced by effort or trauma.

Carbon monoxide poisoning occasionally results in damage to the heart, or aggravates a preëxisting condition, but it does not lead to coronary occlusion. Most cases of cardiac involvement attributed to carbon monoxide are based on insufficient evidence.

While neurocirculatory asthenia usually occurs in persons constitutionally susceptible to strain, in rare instances the onset of symptoms may be related to effort or trauma.

The problem of compensation in heart disease would be simplified considerably if a completely trustworthy history could be obtained in every case.

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HEPARIN AND THROMBOSIS

Harvey Lecture, November 28, 1940

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I WAS very pleased and, of course, highly honored when your President invited me to present to the Harvey Society the results of our work on heparin. In strenuous times like these there is a natural tendency to concentrate our attention on the application of physiological knowledge to the clinical problems of the moment. While I do not wish to infer that the members of our group have not been concerned with the many fundamental physiological and biochemical problems which have been encountered, the fact that heparin is of importance in certain aspects of military surgery has helped to sustain our interest in the subject during the past year.

I am honored this evening by the presence of Dr. Jay McLean, who in 1916 in Professor Howell's laboratory obtained evidence of the presence of the anticoagulant, heparin, in animal tissues. With heparin, as with many other compounds of biological importance, a careful search of the literature reveals the fact that several groups of workers had previously demonstrated the existence of a substance which was probably heparin (Schmidt,[1] Doyon,[2]) but the investigations of McLean[3] were directly responsible for the further studies which have led up to the present situation. It is a privilege to pay tribute also to Professor Howell, who was responsible for so much of the original work on heparin and who anticipated the results of a great many of the relatively recent experiments. Professor Howell's interest and active participation in research on blood coagulation has extended over a period of more than fifty years. In his Harvey Lecture of 1917[4] he describes the researches which led to the isolation of the anticoagulant and sets forth very clearly the important contribution which Dr. McLean made.

Before considering the role of heparin in the prevention of thrombosis I will spend a few minutes attempting to lay a foundation on which this story may be superimposed.

Thrombosis. The term thrombosis is derived from the Greek word θρομβος. It was used by Hippocrates and Galen to describe a blood clot. A clot is, of course, a thrombus, but we distinguish this type from others by terming it a "red thrombus." A thrombus may be formed almost entirely by platelets, and this type is appropriately named a "white thrombus." While most thrombi are of the mixed variety—that is, with both red and white elements—emphasis will be laid this evening on the white thrombi since they almost invariably constitute the nucleus from which the red or mixed forms develop.

The early workers on thrombosis looked upon the process as an intravascular coagulation, and it is only within the last seventy years that the platelets have been recognized as cellular entities and their very special role in thrombosis appreciated. This change in our conception of the process is due to the work of Mantegazza,[5] Hayem,[6] Osler,[7] Bizzozero[8] and others. It is, however, in a very special measure, the findings of Bizzozero which demonstrated that under certain circumstances platelets may accumulate and thus constitute a nucleus for a thrombus. I regret that I will not have time this evening to discuss this work in detail, but this consideration would in any event only demonstrate the pathway by which one arrives at the conclusion that the factors governing platelet agglutination are as yet imperfectly understood.

Coagulation and Platelet Agglutination

The differentiation of these processes was well initiated when Bizzozero observed the agglutination of platelets on the damaged intimal surface of blood vessels and it was advanced when Leo Loeb[9] and others studied the phenomena in various forms of animal life. In certain arthropods, as many of you remember, fibrinogen is lacking and the agglutination process may, therefore, be readily studied uncomplicated by the phenomena of coagulation. In *Limulus polyphemus* the blood contains only one type of cell, the amoebocyte, and it is the agglutination of these which constitutes the protective mechanism against prolonged hemorrhage in these species. My colleague at McGill, Professor John Tait,[10] found a somewhat similar situation in *Gammarus marinus* and noted that cell agglutination was the only obvious process in the formation of a clot. In some other species there are the so-called explosive corpuscles, the rupture of which promotes the formation of a coagulum. True blood coagulation as we see it in mammals is encountered first in certain ar-

thropods, the dekapods. In some of these forms clotting occurs quite rapidly, but in others many hours are required. (It is, I trust, not a sign of advancing years that during the last few weeks I have repeatedly thought of the charming existence one might lead in a secluded laboratory in the South Seas studying the development of these processes and the role of heparin in forms as far removed from man as possible. It is difficult to reconcile these thoughts with those expressed in my opening paragraph. The psychologists will undoubtedly suspect a conflict of emotions.) It is apparent that the two processes, agglutination and coagulation, have been developed side by side during the evolution of the animal species. Agglutination was the earlier of the two and this process persists in the higher forms. It is primarily with this mechanism, and the effect of heparin on it, that we are concerned this evening. It will be necessary to dismiss, with only the most fleeting reference, the whole fascinating question of the action of heparin on blood coagulation, our knowledge of which has been so rapidly advanced by the results recently obtained by Quick; Smith, Warner and Brinkhous; Ferguson and others. It is now well established that heparin may act both as an antithrombin and as an antiprothrombin and that some as yet incompletely identified factor, or factors, present in blood serum is necessary for these actions.

The interrelationship of the agglutination and clotting processes is a fascinating question and they undoubtedly are intimately associated under many conditions. It can, however, readily be demonstrated in mammals that the two mechanisms are separable. One has only to watch the clotting of blood from which the platelets have been removed, or the formation of a white thrombus in which no fibrin is detectable by the methods available, to conclude that there are at least no obvious indispensable relationships between the processes. It remains possible, however, that further work will reveal that some process analogous to that of blood clotting plays a part in the agglutination of the platelets. Many other theories which I will not even enumerate have, of course, been proposed, and it will certainly be necessary to understand this phenomenon much more clearly than we do at present before we can hope to decide by what means heparin affects it.

Heparin

There is little doubt that the method of presentation of a scientific subject which makes the greatest appeal to a lecturer is to follow a trail

which he has helped to make. In availing myself of this privilege this evening I am adopting the suggestion which your President made in his invitation, but I wish to make it very clear that the members of our group have joined forces with the other workers in this field at a point separated from the origin of the trail by many years of hard and productive work. At this particular point, however, progress seemed to be very slow and the advance was undoubtedly hindered by two obstacles. A uniformly potent preparation of heparin which could safely be given in adequate quantities to experimental animals and to human subjects was not available, and convincing evidence that heparin inhibited platelet agglutination as well as coagulation had not been secured. While I will present the results of the Toronto work, which I initiated in 1929, in considerable detail I am anxious not to neglect the studies of Fischer in Copenhagen, of Jorpes, Bergström, Holmgren, Wilander and others in Stockholm, and of Chargaff and Olson and others in this country.

Preparation and Chemical Properties of Heparin

For the past eleven years Dr. Arthur Charles, working first in the Department of Physiology and then in the Connaught Laboratories in Toronto, has been exploring the preparation and purification of the anticoagulant. Dr. Charles found that beef lung was the cheapest commercial source and this tissue has been used exclusively for many years for the preparation of heparin. When adequate amounts of crude heparin were available, attempts were made to isolate the active principle. In 1933 Charles and Scott[11] in Toronto and Schmitz and Fischer[12] in Copenhagen reported the isolation of a crystalline heparin. The Toronto workers obtained it as a sodium salt, the Danish workers as a brucine salt. Neither of these procedures lent themselves readily to large scale production. In 1936 Charles and Scott[13] reported on the preparation of a crystalline barium salt (Fig. 1). This salt can be obtained in good yields and large amounts of heparin can be purified by this method. Heparin has been obtained as the crystalline barium salt from various other tissues of the ox and from other species. Jorpes,[14] as a result of fractionation studies on impure beef heparin, has suggested that the crystalline anticoagulant is not a pure substance but a mixture of two closely related compounds which differ in their sulphate content and activity. Studies of crystalline barium salt do not support this view. In Table I

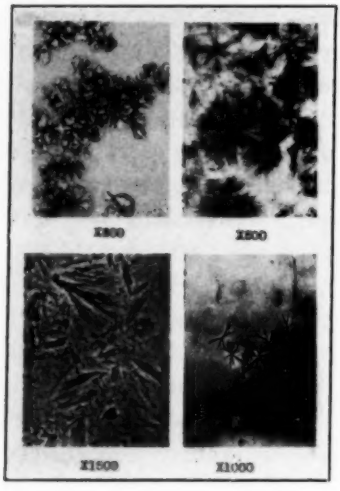

FIG. 1. Crystalline barium salt of beef heparin. (Charles and Scott.) × 500 and × 1500 are magnifications of the same crystals as in × 200.

TABLE I

Starting material	Methods	Per cent Ash	Potency	Per cent N
			u./mg.	
Beef lung	$CdCl_2$—$(NH_4)_2CO_3$	33.1	98	2.13
" "	$CdCl_2$—Benzidine	33.8	98	2.04
" "	Charcoal—Benzidine	33.7	104	1.89
" "	Charcoal—$(NH_4)_2CO_3$	33.1	97	1.90
Beef liver	$CdCl_2$—$(NH_4)_2CO_3$	33.8	100	2.20
" "	$CdCl_2$—Benzidine	33.2	98	2.01
" "	Charcoal—$(NH_4)_2CO_3$	33.3	98	1.90

some data obtained on beef heparin prepared from different tissues and by different methods are given. This is taken from a recent paper by Charles and Todd.[15] These samples were all prepared as the crystalline barium salt and in each case over 80 per cent of the activity present in the original crude heparin was obtained in the crystalline form. The ash and nitrogen contents and the potency of the heparin obtained from

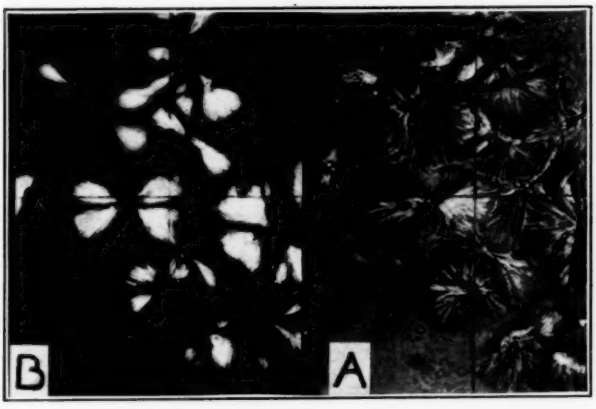

FIG. 2. Crystalline barium salt of beef heparin. A. With plane polarized light. B. With crossed Nicol prisms.

these various tissues by different methods are the same. These findings support the conclusion that the crystalline salt is a chemical individual. (Furthermore, it has seemed to the chemists in our group that Jorpes' own data scarcely bear out his contention that the activity of heparin is due to the sulphate-containing material in the preparation. In experiments designed to prove this point, he recovered 70 per cent of the sulphur and 50 per cent of the activity in his various fractions, while 30 per cent of the sulphur and 50 per cent of the activity were lost in the process.) The significance of the crystalline barium compound is the one point in which the results of our group, i.e., of Charles and Scott, differ from those of the Swedish workers. In most cases the findings of the two groups have been in accord. Some recent pictures of the crystalline heparin made by Dr. Hamly, Department of Botany, University of Toronto, show the appearance of the crystals in plane polarized light and through crossed Nicol prisms (Fig. 2).

A brief review of the chemistry of heparin establishes the following facts. Howell[16] demonstrated that heparin is of a carbohydrate nature. Charles and Scott established the presence of nitrogen, and Jorpes the presence of sulphur in the form of a sulphuric acid residue. This latter finding led Jorpes to advance the theory that heparin is a chondroitin polysulphuric acid and this is the basis of all recent views on the chemi-

cal structure of heparin. Heparin differs markedly, however, from the chondroitin and mucoitin sulphuric acid already isolated, both, of course, in its physiological action and in its elementary analysis (N: S ratio 2: 5 instead of 1: 1). Also Meyer[17] has found that his enzyme which splits mucoitin sulphuric acid has no effect on heparin. It follows, therefore, that conclusions regarding the nature of the carbohydrate portion of the molecule must be based on actual chemical studies of pure heparin and not on analogy between its structure and that of the known carbohydrate sulphuric acids. It was established by Jorpes and Bergström[18] that heparin contains glucosamine and a uronic acid.

The recent investigation of Charles and Todd, working in Manchester, has thrown new light on the problem of the chemistry of heparin. On the basis of the analytical values which they obtained with the crystalline barium salt, they suggest the formula shown in Fig. 3. This

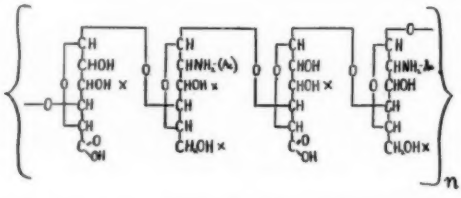

Fig. 3. Suggested basic structure of beef heparin. (Charles and Todd.)

is in conformity with the results of Reinert and Winterstein who have had no difficulty in preparing a crystalline heparin which has the same potency as the Toronto product. It is essentially the classical formula for mucoitin sulphuric acid proposed by Levene which consists of two glucosamine and two uronic acid residues. Levene[19] has suggested that this is polymerized by repeated glucosidic linkages to give a long chain structure similar to that of starch. Since there are five sulphate groups for each two amino groups, the basic unit of heparin presumably contains the four hexose groups. The five sulphate groups are probably disposed, Charles and Todd feel, as shown in the formula. The analytical data do not show clearly the degree of acetylation of the amino groups. The two carboxyl groups of the uronic acid molecules are either free or lactonized. The uronic acid is unknown. The crystalline salt is thought to be the barium salt of the sulphate groups rather than the carboxyl. Recently,

Jaques and Waters[20] in my laboratory have isolated the crystalline barium salt of heparin from dog liver by the same procedure as that applied to beef tissues. Dog heparin appears to be slightly different from that obtained from beef tissues. It has a higher potency and a lower sulphur content. Since its general chemical properties, i.e., solubility, crystalline form and so on, are the same as for beef heparin, there appears to be only a slight chemical difference between the two substances. Even more recently Jaques[21] has prepared crystalline heparin from a number of species and I am indebted to him for the data in the following table (Table II). It is thus established that, while the heparin for any one species

TABLE II

Potency, Sulphur and Nitrogen Content of Heparins from Different Species
(Calculated for the free acid)

Species	Potency	Per cent sulphur	Per cent nitrogen
Dog	345	14.0	3.0
Beef	154	14.4	2.6
Pork	70	14.1	2.4
Sheep	32	14.7	2.8

All determinations were made on the crystalline barium salt (prepared by the procedure of Charles and Scott) and the corresponding values for the free acid were calculated by correcting for the water of crystallization, barium and ammonium-nitrogen present. The crystalline barium salt of beef heparin has a potency of 100 units per mg.

is a chemical entity, a number of different heparins exist in the various species.

The groups in the heparin molecule responsible for its extremely high anticoagulant activity are, of course, of great interest. Both Howell and Fischer[22] concluded that the uronic acid residues were responsible. Jorpes believes that it is the sulphate groups. A safer position, however, is that the anticoagulant activity is dependent upon all the groups in the molecule and their appropriate arrangement. The removal of *sulphates*, amino nitrogen or carboxyl groups causes almost complete disappearance of the anticoagulant activity. It can be shown that type substances containing any of these groups possess anticoagulant activity but none of these approaches the potency of heparin. The most potent substitute has

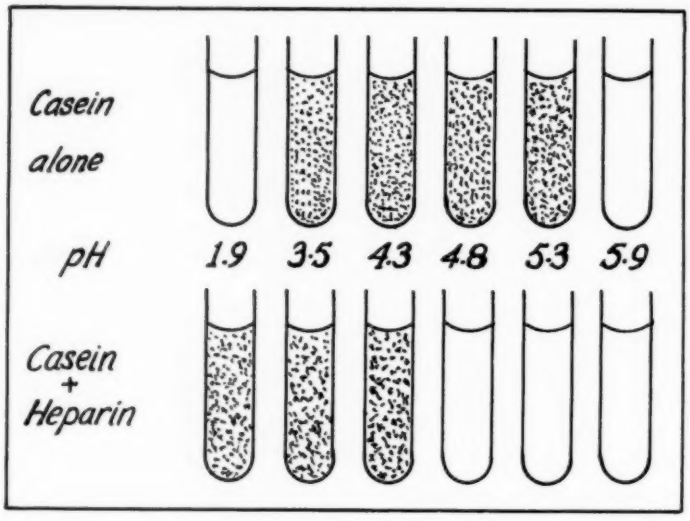

FIG. 4. Effect of heparin on the isoelectric point of casein. 10 mg. casein and 1 mg. heparin in each 100 cc. of N/100 acetate buffer. (Jaques.)

perhaps one-tenth the activity of heparin and a much greater toxicity.

The most significant biochemical property of heparin is its power to react with protein. This phenomenon was discovered and carefully investigated by Fischer.[23] He concluded that heparin combines with proteins on the acid side of the isoelectric point. He demonstrated by suitable means that compounds could be formed with casein, hemoglobin, liver proteins and protamine. Fig. 4, prepared for me by Mr. Jaques, illustrates the reaction with casein. Casein is insoluble at its isoelectric point, pH 5, but the heparin-casein compound is soluble at this hydrogen ion concentration. The reaction of heparin with proteins may result in inactivation of the heparin if the protein used is able to compete with the clotting system for the heparin. Chargaff and Olson[24] have studied the reaction of heparin with protamine and have developed a simple test for heparin in blood and a means of neutralizing heparin both *in vivo* and *in vitro*. This reaction provides a rapid quantitative test for heparin in blood. These observations have been confirmed and somewhat extended by the members of our own group. The procedure has

been applied clinically by the Swedish workers for the neutralization of heparin, but we would recommend a very cautious approach to this use of protamine in clinical studies.

The Standardization of Heparin

At the present time there is a great deal of confusion in the literature due to the fact that there is no universally accepted unit of heparin. Reinert and Winterstein reported the results of comparisons between the various units. Without going into the details of these different units, one apparently represents the activity of about 1/100 mg. of the crystalline barium salt of heparin, another one about 5/100 mg. and a third 1/1250 mg. The Connaught Laboratories of the University of Toronto have donated 100 grams of the crystalline barium heparin to the Committee on Biological Standardization of the League of Nations, with the suggestion that the unit be set as the activity contained in 1/100 mg. of this material.

Toxicity of Heparin

The fact that heparin forms stable salts with proteins with great ease is probably the explanation of the difficulty of removing protein substances completely from preparations of the anticoagulant. The explanation of the toxic effects of certain preparations of heparin may lie along this line. Howell and Mason relinquished their clinical trials because of toxic effects. The same problem was encountered in the first clinical trials in Toronto and in Stockholm. A high fever may be produced by impure preparations and gastrointestinal symptoms are common. When heparin is prepared from a crystalline barium salt the material is usually non-toxic but, on certain occasions, very objectionable reactions have been produced. Recently, through the work of Charles, Jaques and McHenry in Toronto, it has been possible to prepare products which are consistently free from these effects. Other groups may have had similar good fortune.

The Site of Formation of Heparin

As we have seen, heparin was first prepared from the liver, but Howell had also obtained small amounts from muscle, lymph nodes and blood. In 1933 Charles and Scott, using their method which gave better

yields, isolated highly active heparin from lungs, spleen and kidneys. The lung was found to be particularly rich. More recently, Jaques and Charles have secured relatively large yields from intestinal mucosa. The physiological significance of the presence of such relatively high concentrations of heparin in the liver, lung and intestinal mucosa, is as yet unknown.

The histological and chemical contributions of Jorpes, Holmgren and Wilander[25] to our knowledge of (1) the source of heparin in the body and (2) the physiological function of the mast cells of Ehrlich deserves very special mention. The function of these cells has been debated since their discovery by Paul Ehrlich in 1877. The cells are characterized by the metachromatic staining of their granules by basic aniline dyes. They have a wide distribution but many investigators have stressed the fact that they are met with abundantly in connective tissue which is rich in blood vessels. It has been suggested that the mast cells are single-celled glandular organs of the connective tissue.

The granules of the mast cells are soluble in water (Ehrlich). Lison[26] found that high molecular sulphuric acid esters or polysaccharides produce the metachromatic staining (chondroitin sulphuric acid found in cartilage and elsewhere gives this color). Jorpes showed that heparin gave a similar reaction with toluidine blue and Bergström[27] noted the same color when the dye was mixed with synthetic sulphuric acid esters of carbohydrate. When toluidine blue was applied by Jorpes to various blood vessels, the characteristic staining was observed but proof that this was due to heparin was required (Fig. 5). Holmgren and Wilander, using this dye as a histological stain, found that the color appeared in the mast cells of Ehrlich which are found mainly in connective tissue near capillaries and in the walls of the larger blood vessels. The granules in the mast cells showed greater affinity for the dye than cells containing chondroitin sulphuric acid and the tint appeared to be somewhat different. Wilander,[28] using the method of Charles and Scott, found a very good correlation between the heparin content of various tissues and the number of mast cells. It thus appears that a new and fascinating chapter of histology and physiology is being written.

Liberation of Heparin in Peptone and Anaphylactic Shock

The blood in peptone shock may be incoagulable (Schmidt-Mülheim and Albertoni, 1880) and many theories have been entertained in the

FIG. 5. Mast cells stained through injection of a diluted solution of toluidine blue into the subcutaneous tissue of the rat. (Jorpes.)

search for an explanation. Howell[29] and Quick[30] have, however, obtained strong evidence in favor of the appearance of heparin during the shock. More recently, Jaques and Waters have neutralized with protamine the anticoagulant which appears in the blood, and Wilander has prepared highly active heparin from the blood of animals in peptone shock. Wilander has secured evidence that this anticoagulant comes, in part at least, from the mast cells in the liver (Figs. 6 and 7).

In 1909 Biedl and Kraus[31] found that the blood became incoagulable in anaphylactic shock. Since that time a great many investigators have studied the problem and almost every factor in the clotting process has been suspected. Quite recently Eagle, Johnston and Ravdin[32] have obtained evidence that the antithrombin content of blood was greatly increased. They suspected heparin but did not prove its presence. Waters, Markowitz and Jaques[33] have shown that the clotting time of blood in anaphylactic shock can be reduced to normal value by the addition of protamine. Protamine neutralizes the effect of heparin by forming with it an inactive salt. Jaques and Waters have been able to isolate heparin in crystalline form from the blood of the shocked animals. The amount of heparin in the liver showed a marked fall (Fig. 8).

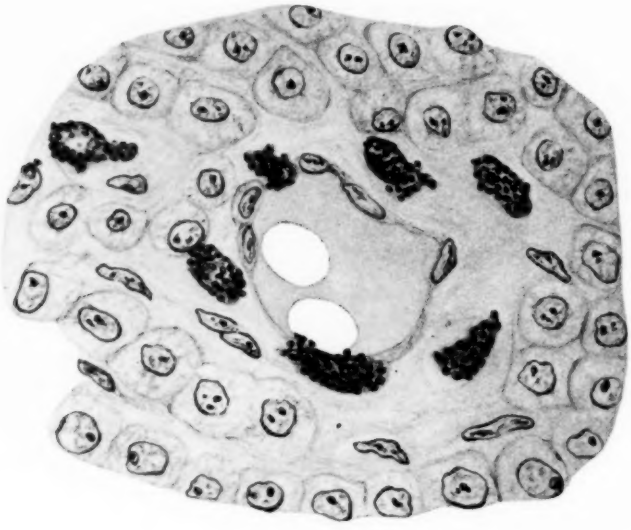

FIG. 6. Mast cells in the liver of a normal dog. The cells contain well fixed granules. The mast cells are grouped around a small blood vessel. (Wilander.)

FIG. 7. Mast cells in the liver of a dog after peptone shock. The cells contain few granules which are small and for the most part faintly stained. (Wilander.)

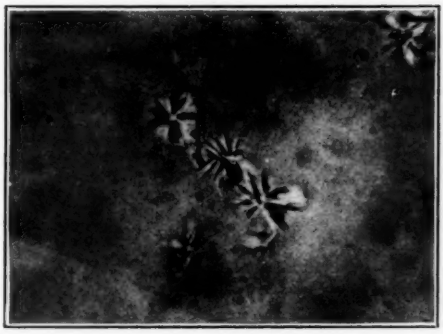

FIG. 8. Crystalline barium salt of heparin isolated from blood of dog in anaphylactic shock; magnification × 450. (Jaques and Waters.)

EFFECT OF INJECTION OF HEPARIN

The effect of heparin *in vivo* is generally followed by the clotting time. The relationship between heparin concentration and dosage has been worked out for the dog by Jaques[34] and for humans by Crafoord.[35] A logarithmic relationship is obtained, i.e., log T against log dose equals a straight line. The effect of a given dose of heparin on the clotting time varies greatly from individual to individual. Crafoord has observed clinically that the curve changes in the same individual after operation; the heparin becomes less effective and he suggests that this may be a valuable clinical test to indicate a need for heparin. By such curves the heparin concentration present in the blood after injection can be calculated. Single injections of heparin, unless large enough to raise the clotting time to undesirable heights, have only a transient effect on the clotting time. Hence heparin is best administered as a continuous intravenous injection, and situations may arise in clinical practice in which the physician is well pleased that the clotting may be returned to normal limits very rapidly, simply by stopping the intravenous infusion.

After a lecture on heparin to a surgical group I was asked by one of the members if the subcutaneous administration of heparin was a safe procedure. I explained that we had reported the occurrence of subcutaneous hemorrhages in several animals of a large series and for this rea-

son the subcutaneous route, in human subjects, was not recommended. He apparently believed in testing the matter on his own patients because he then stated that he had frequently given subcutaneous injections of heparin and had encountered no difficulty! The subcutaneous route may, however, advantageously be used in small animals, and we have experimented with substances which delay the absorption.

The relationship between the level of clotting time reached and the rate of injection appears to be quite constant amongst individuals. At present, this has only been established for the dog. In this way it is possible to maintain the heparin level in the blood and a constant raised clotting time by a continuous injection. It is usual to give a single injection when the administration is started in order to raise the clotting time to the new level. The actual clotting time for a given concentration of heparin varies with the individual.

Heparin disappears rapidly from the circulation. While some excretion of heparin occurs in the rabbit (Wilander), none occurs either in man (Reinert and Winterstein)[36] or in the dog (Jaques). Its rapid destruction may be due to an enzyme, heparinase, which Jaques,[37] working in my department, has recently discovered and described. The enzyme has a pH optimum between 5 and 6 but its exact physiological role is as yet quite unknown.

The Physiological Role of Heparin

Howell suggested that heparin was responsible for the fluidity of the blood. The low values for the heparin content of blood and high ones for tissues found by Charles and Scott led Mellanby[38] to suggest that heparin maintained the fluidity of the blood by being continually passed into it to neutralize the kinase from tissue breakdown. (Chargaff et al. have shown that heparin may appropriate the protein from the cephalin-protein complex which is kinase.) The position of the mast cells (in the vessel walls) also supports Mellanby's view. These findings suggest that heparin has a definite physiological role. There is little evidence, however, that heparin is a constituent of normal blood (Quick[30]). The results obtained in attempts at isolation, the relationship between clotting time and heparin concentration, and the effect of protamine on the normal clotting time suggest that the heparin content of normal blood might be of the order of 1/10 unit per cc. At present, however, none of these methods is sensitive enough to detect heparin concentrations of this

order. Therefore, no experimental evidence which is free of serious objections has been obtained. At present the heparin concentration in normal blood and the physiological role of heparin must be considered an open question, but interesting developments in this field may be predicted.

Heparin and Thrombosis

It appeared to us that adequate proof would have to be provided that heparin prevented thrombosis, i.e., platelet agglutination, before an extended clinical trial could be considered justifiable. The results of experiments conducted by Shionoya suggested that heparin was not effective in preventing agglutination of platelets, but, as Professor Howell suggested at the time, there was a strong possibility that more highly purified heparin would exert an effect. Gordon Murray of the Department of Surgery, with Jaques, Perrett and myself[39] found that thrombi forming on the intimal surface of veins which had been injured by mechanical or chemical means could be completely prevented by the adequate administration of purified heparin. After three days of continual heparinization, the vein was completely healed and there was no indication that a thrombus would form subsequently at the site which had been injured. In a later paper the formation of white thrombi was studied (Best, Cowan and MacLean[40]). It was found that in dogs, cats and monkeys, the agglutination of platelets could be inhibited or prevented when large amounts of heparin were employed. It may be remarked here that much higher concentrations of heparin were required to prevent agglutination of platelets in glass cells than in the body. In the third series of investigations D. Y. Solandt and I[41] produced coronary thrombosis by isolating the coronary artery and injecting sodium ricinoleate within the lumen. This material was kept in contact with the intima for five minutes and the clamps on the vessel were then released. In almost every case when no heparin was used a thrombus was present, and in the heparinized series this was a rare occurrence. The fourth series, by Solandt, Nassim and myself[42] had to do with the production of cardiac mural thrombi and the prevention of their formation by the administration of heparin. A technique was evolved by which large mural thrombi could be regularly produced in the lumen of the left ventricle. The endocardium of this cavity was injured by injecting sodium ricinoleate and the myocardium was damaged by ligating the an-

terior descending branch of the left coronary artery. The findings show that without heparin there was a rapid formation of thrombi, but none was seen in those experiments in which the heparin was given well before the injury was produced. These experimental results establish the fact that heparin is extremely effective in preventing platelet agglutination under a variety of experimental conditions. Solandt and I[43] have recently shown that with large doses of heparin the effect on platelet agglutination, unlike that on the clotting time which develops after a short latent period, may require from 15 to 50 minutes to become obvious under certain experimental conditions. This point should be kept in mind in experimental or clinical studies.

Physiological and Clinical Uses of Heparin

The method developed by Charles and Scott is now used, in its entirety or in part, for the preparation and purification of all the highly potent heparin available on this continent or in Europe. The provision of an adequate supply of this material has made possible many new experimental and clinical investigations. To illustrate some of the newer physiological applications I may cite the investigations on exchange transfusions carried out in Toronto. The development of this method as we now use it was initiated by Dr. William Thalhimer and he collaborated with us in the first experiments which I will refer to in a moment. A good illustration of the usefulness of the exchange transfusion technique in highly heparinized animals is provided by recent experiments of Solandt, Nassim and Cowan.[44] The blood of a dog made hypertensive by the Goldblatt technique was exchanged at a rapid rate by means of a special pump (Solandt and Robinson)[45] with that of a nephrectomized donor. This procedure enabled these investigators to demonstrate for the first time the presence of a pressor substance in the systemic blood of a hypertensive animal (Fig. 9). The presence of this substance had, of course, been previously demonstrated by other workers in the blood from the renal vein. Solandt and I[46] have been using this technique to investigate the toxemic theory of shock by exchanging the blood of a normal animal with that of one suffering from traumatic shock. The first of our series of experiments on exchange transfusions was, however, conducted with Thalhimer.[47] In these experiments we exchanged the blood of nephrectomized and normal dogs and noted the rapid lowering of the urea content of the blood of the uremic animal

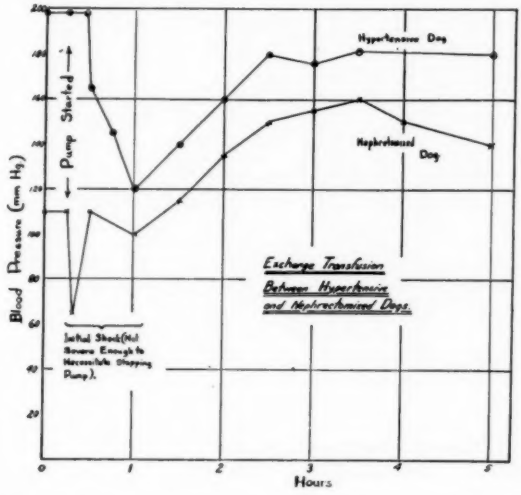

FIG. 9. Exchange transfusion between hypertensive and nephrectomized dogs. (Solandt, Nassim and Cowan.)

and a great increase in the excretion of urea in the normal (Fig. 10). In the report of this work we suggested that a clinical application might some day be made. We have been extremely interested to learn of the work of Duncan, Tocantins and Cuttle[48] (Fig. 11), who exchanged the blood of uremic patients with that of normal subjects. They secured a very definite increase in the nitrogen excretion of the normal subject. In the two uremic patients which they studied in detail the authors suggested that there was a definite clinical improvement. These findings encourage the hope that some day the technique may be perfected by which the kidneys or perhaps some other organ of normal subjects may be made available, as it were, to patients in whom there is a serious *but presumably transient* deficiency in some physiological function.

A great many patients in Toronto, in Stockholm and elsewhere have been heparinized during the so-called danger period after operative procedures which have in the past been followed by a relatively high incidence of embolic phenomena. It is obviously extremely difficult to secure scientific proof of the influence of heparin under these conditions. The results have not, however, been unfavorable and in many

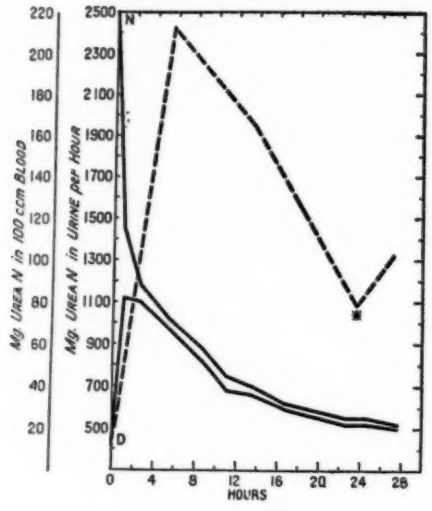

FIG. 10. Exchange transfusion continued over full period. Continuous line = blood; interrupted line = urine; N = nephrectomized dog; D = normal dog; * = catheter plugged. (Thalhimer, Solandt and Best.)

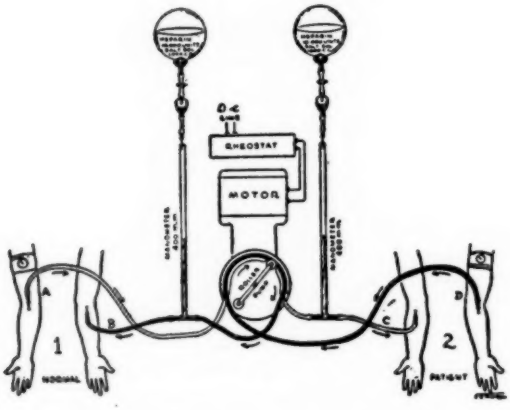

FIG. 11. Diagram of the apparatus. 1A, delivering vein; 1B, receiving vein of the normal individual; 2D, delivering vein; 2C, receiving vein of the uremic patient. The 2 tubes rest exactly superimposed in a semi-circle around the periphery of the roller pump. (Duncan, Tocantins and Cuttle.)

individual cases the clinicians have been convinced that thrombus formation was prevented. We must always keep in mind the possibility that thrombi may be present before the heparinization is initiated. There is no evidence that heparin increases the likelihood that emboli will be broken off. Its action is to prevent the formation of thrombi and not to dissolve those already formed.

The results of Murray's work in Toronto, that of the surgical group in Stockholm, and of various surgeons in this country, leave no doubt that heparin is a valuable adjuvant in certain types of vascular surgery. Murray's work[49] on the substitution of veins for arteries in certain cases of arterial aneurysm, the removal of emboli which have severely damaged the intimal lining of blood vessels, and the repair of severed arteries, furnish dramatic examples of the advance in surgery which the purified anticoagulant has helped to make possible. Similar results have been obtained in various clinics in this country.

There seems to be little doubt from the results reported by Holmin[50], Ploman[51] and other Swedish workers that heparin is very useful in the treatment of thrombosis of the central vein of the retina. There will undoubtedly be an opportunity to test these conclusions in a large number of clinical cases.

In 1939 Kelson and White[52] treated a number of cases of subacute bacterial endocarditis with sulphapyridine in combination with heparin. Kelson has continued this work and while he feels that favorable results, in some cases, have followed the use of heparin when the chemotherapeutic treatment was effective in lowering the temperature and sterilizing the blood, he also states that the value of heparin has not been conclusively established.

Heparin has been used in a few cases of coronary thrombosis in human beings, but not as yet in a scientific manner. It would appear that the only way to determine whether or not it is of value in this condition is to heparinize every other patient of a very large series. Judging from the experimental work (Solandt and Best) the incidence of mural thrombus formation and the extension of coronary thrombi, if this occurs, would be inhibited. If there were any other therapeutic agent available for the treatment of this condition, the use of a substance which demands such careful supervision as heparin, could not perhaps be justified. Since, however, it is the only material available which prevents the growth of thrombi, it would appear that the clinical cardiologist

might explore its possibilities in a carefully controlled series of observations. He will, of course, have no preconceived ideas with regard to its therapeutic value in the condition which he is studying, but he may start his investigations with the knowledge that, if given in adequate amounts, further thrombus formation will be prevented. He will also have to bear in mind that heparin, like many other effective weapons, is a "two-edged sword" and that its function is to prevent coagulation as well as to inhibit thrombus formation.

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DEATHS OF FELLOWS

FARLEY, OLIN EVERETT: 140 East 54 Street, New York City; born in Lowell, Massachusetts, January 24, 1892; died in Harrison, New York, August 5, 1941; graduated in medicine from McGill University, Montreal, in 1915; elected a Fellow of the Academy April 5, 1934.

Dr. Farley was surgeon to the Manhattan Eye, Ear and Throat Hospital and consultant in ophthalmology to the Holy Name Hospital at Teaneck, New Jersey. He was a Fellow of the American Medical Association and a member of the County and State Medical Societies.

FRY, HENRY JACOB, Ph.D.: Westport, Connecticut; born in Lancaster County, Pennsylvania, May 2, 1892; died in Westport, Connecticut, August 17, 1941; received the degree of Doctor of Philosophy from Columbia University in 1925; elected an Associate Fellow of the Academy November 6, 1930.

Dr. Fry was professor of biology at the Washington Square College, New York University, from 1930 to 1933, having been appointed as instructor in 1923. From 1931 to 1938, he was on the faculty of the New School for Medical Research.

JOACHIM, HENRY: 1111 Park Avenue, New York City, and 871 Park Place, Brooklyn, New York; born in Brooklyn, April 16, 1883; died in New York City, August 18, 1941; graduated in medicine from Cornell University Medical College in 1904; elected a Fellow of the Academy, November 2, 1922.

Dr. Joachim was associate physician on the staff of the Jewish Hospital, 1911-18; attending physician and clinical professor of medicine to the Long Island College Hospital, 1918-31; and head of the medical department at the Greenpoint Hospital, 1918-22. Since 1922, Dr. Joachim was chief of the medical staff of the Israel Zion Hospital and Beth Moses Hospital, and since 1933 he was medical director of the Cumberland Hospital and the Jewish Sanitarium and Hospital for Chronic Diseases. He was also consulting physician to the Sydenham Hospital.

Dr. Joachim was a diplomate of the American Board of Internal Medicine, a Fellow of the American College of Physicians, a Fellow of the American Medical Association and a member of the County and State Medical Societies. He was a for-

mer president of the Kings County Medical Society and the Williamsburg and New Utrecht Medical Societies.

KAST, LUDWIG: 525 Park Avenue, New York City; born in Vienna, Austria, March 2, 1877; died in New York City, August 14, 1941; graduated in medicine from the Medical Faculty of the University of Prague, Austria, in 1903; received the degree of Sc.D. from Syracuse University in 1934; elected a Fellow of the Academy, April 7, 1910.

Dr. Kast came to the United States in 1906, after postgraduate work in Vienna, Prague, Munich, London and Berlin, to continue his research in the physiology and pathology of digestion at the Rockefeller Institute.

In 1907, he was appointed instructor in medicine at the New York Post-Graduate Medical School and Hospital and was made assistant professor in 1909, and full professor in 1914. He became a member of the Board of Directors of the institution in 1912, and since 1914 had continued as an active Trustee of the school, specializing in teaching and research in problems of internal medicine and education. He also contributed to many medical publications on problems of experimental and clinical medicine.

In 1909, he was appointed secretary to the national committee of the United States of the International Committee on Postgraduate Medical Education, a position which he held until 1914 and in which he was largely instrumental in establishing many contacts with European medical universities for exchange of American teachers and students. His research in internal medicine and medical education soon made him widely known and in 1930 he became the President of the Josiah Macy Jr. Foundation for medical research.

Dr. Kast was a Fellow of the American Medical Association, a member of the American Roentgen Ray Society, the American Gastroenterological Association, the Society for Experimental Biology and Medicine, the New York Pathological Society, the Harvey Society and the County and State Medical Societies. He was a lieutenant-colonel in the United States Medical Officers Reserve Corps and in honor of his medical researches had been decorated by the Belgian Order of the Crown and the Palme Academique of the French Academy.

Dr. Kast, who first proposed the establishment of the Graduate Fortnight of the Academy, which was instituted in 1928, continued to give inspiration to this enterprise until the time of his death. In honor of the founder of these Fortnights, the opening lecture of the Fortnight is designated the "Ludwig Kast Lecture."

NILES, HENRY D.: 114 East 54 Street, New York City; born in Brooklyn, N. Y., November 18, 1901; died as the result of an automobile accident near Fort Peck, Montana, August 27, 1941; graduated from the Johns Hopkins University Medical School in 1925; elected a Fellow of the Academy, November 2, 1933.

Dr. Niles was a member of the State and County Medical Societies, the American Academy of Dermatology and Syphilology, the American Dermatological and Metropolitan Dermatological Societies, and a member of the Alumni of New York Hospital. He was also Assistant Physician to the New York Hospital, Assistant Dermatologist and Syphilologist to the Post-Graduate Hospital, Dermatologist and Syphilologist to the Out-Patient Department of the Post-Graduate Hospital, Senior Dermatologist to the West Side Hospital and to the Out-Patient Department of the West Side Hospital.

SOUR, BERNARD: 1124 Park Avenue, New York City; born in Shreveport, Louisiana, September 17, 1869; died in New York City, May 7, 1941; graduated in medicine from the College of Physicians and Surgeons, Columbia University, in 1893; elected a Fellow of the Academy February 6, 1902. He was a Fellow of the American Medical Association and a member of the State and County Medical Societies.

STERN, ABRAM RICHARD: Danbury, Connecticut; born in New York City, July 21, 1874;

died in New York City, May 8, 1941; graduated in medicine from the College of Physicians and Surgeons, Columbia University, in 1899; elected a Fellow of the Academy January 5, 1905. He was a member of the American Medical Association and the State and County Medical Societies.

STRONG, ARCHIBALD MCINTYRE: 180 Ft. Washington Avenue, New York City; born in Montclair, New Jersey, June 16, 1881; died in New York City, July 21, 1941; received the degree of A.B. from Princeton in 1904 and graduated in medicine from the College of Physicians and Surgeons, Columbia University, in 1908; elected a Fellow of the Academy January 6, 1938.

Dr. Strong was associate physician to the Presbyterian Hospital, a Fellow of the American Medical Association, a member of the New York Society for Clinical Psychiatry and a member of the County and State Medical Societies.

WOODRUFF, WALTER STUART: 421 Huguenot Street, New Rochelle, New York; born in Dunkirk, New York, April 10, 1883; died in Colebrook, Connecticut, August 19, 1941; graduate in medicine from the University of Michigan in 1906; elected a Fellow of the Academy January 6, 1927.

Dr. Woodruff was attending surgeon to the Mount Vernon Hospital, 1910-1922; instructor in otolaryngology at the University of Michigan, 1922-1925; attending otolaryngologist to the New Rochelle Hospital, 1925-1938, the time of his retirement; and consulting rhinologist to the Ossining Hospital, 1926-1931.

He was a diplomate of the American Board of Otolaryngology, a Fellow of the American College of Surgeons, a member of the American Academy of Ophthalmology and Otolaryngology, a former president of the Westchester County Medical Society, and a member of the Medical Society of the State of New York, and the New Rochelle Medical Society.

ZIEGLER, JEROME MARTIN: 144 East 90 Street, New York City; born in New York City, June 23, 1894; died in New York City, August 25, 1941; graduated in medicine from the College of Physicians and Surgeons, Columbia University in 1918; elected a Fellow of the Academy, April 7, 1927.

Dr. Ziegler was a member of the State and County Medical Societies, a member of the American Medical Association and the Alumni of the Mount Sinai Hospital. He was Associate Surgeon to the Montefiore, Beth David, Sydenham and Riverside Hospitals, and Assistant Surgeon and Surgeon-in-Charge of the Urological Clinic at the Mount Sinai Hospital.

Since 1926 Dr. Ziegler was a Police Department Surgeon in Queens County.